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Impact of anxiety, stress and depression related to COVID-19 pandemic on the course of hereditary angioedema with C1 inhibitor deficiency

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Abstract:

Background: Hereditary angioedema (HAE) attacks can be provoked with psychological factors. The aim of this study was to assess the effects of anxiety, depression and stress related to COVID-19 pandemic on disease activity of HAE patients during the quarantine period (QP) and the return to normal period (RTNP).

Methods: This study was conducted between March 2020 and September 2020 in four allergy centres. Demographic, clinical features and mental health status were evaluated in QP (from March to the beginning of June) and RTNP (from June to the beginning of September) applied by the government. The 10-point visual analogue scale (VAS10) was used to define the severity of HAE attacks. Depression-Anxiety- Stress Scale-21 (DASS-21) and Fear of COVID-19 (FC-19) scales were performed to assess mental health status.

Results: 139 HAE patients were included in the study. In QP, median attack numbers and median VAS10 scores were 5 (min-max: 0-45) and 6 (min-max: 0-10), respectively. HAE attack numbers, DASS-21 stress, anxiety, depression and total DASS-21 scores, as well as FC-19 scores were higher in QP than RTNP ($p=0.001$, $p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). However, there was no difference in attack severity scores between the two periods ($p>0.05$).

Conclusions: This study revealed that the restriction measures during COVID-19 outbreak causes an increase in the number of HAE attacks in relation to anxiety, depression, stress and fear of

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COVID-19 pandemic. Therefore, it is important to provide psychological support to HAE patients during the pandemic.

Keywords*: coronavirus, COVID-19, hereditary angioedema, pandemic, psychological effects*

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Introduction

Health crises like a pandemic have deep psychological effects on human beings[1,2]. After the outbreak of Coronavirus disease 2019 (COVID-19) was declared as an international public health crisis on January 30, 2020 and a pandemic on March 11, 2020 by the World Health Organization[3], the first case in Turkey was reported on March 11, 2020 by the Turkish Ministry of Health (MoH).

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People throughout the world were restricted to their homes due to nation-wide lockdowns and limited quarantine applications which were implemented to set the transmission of the disease under control [4]. Eventually, this unprecedented development has caused diverse clinical consequences including anxiety and stress in populations [5].

Several studies have been published to evaluate susceptible individuals with chronic diseases for more severe COVID-19 outcomes. Patients with cardiovascular diseases, diabetes, chronic respiratory syndrome, immunosuppression, cancer have been determined as high vulnerable groups for severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and predisposition to COVID-19 in such conditions have been recently investigated [6]. The clinical implications of COVID-19 on patients with chronic diseases have also been reported [7,8] however its impact on orphan diseases like hereditary angioedema (HAE) have not been evaluated so far. Recently, a case series of SARS-Cov-2 infected HAE patients have been published but still the psychological effects of the pandemic and related restrictions on HAE patients are unknown [9].

HAE with C1-inhibitor deficiency (C1-INH HAE) as a rare autosomal dominant disorder is characterized by unpredictable potentially life-threatening recurrent attacks of swelling in larynx, abdomen, extremities, face and genitalia without pruritus[10,11]. Although most attacks occur spontaneously, mechanical trauma, infection, hormonal changes, emotional stress, anxiety and depression are possible triggers [12-14]. Stress and anxiety are the most frequent emotional factors influencing patients' attacks [13,15]. HAE varies in its course and differs individually. There are objective patient- reported outcome tools for assessing HAE activity and QoL that are recommended to be applied during the disease course[16].

Recent data put forward the possible immunological background of the emotional changes seen in animal models for HAE[17-20] . However, we can assume that various environmental stimuli and unpredictable nature of the disease can also influence the development of emotional changes in HAE patients. HAE patients are susceptible to the development of anxiety and depression due to their illnesses [21]. Recently, published data have suggested that HAE impairs the quality of life and affects social activities even between episodes [21,22]. Although recent data about the role of stress

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and psychological factors in HAE are limited, it is so interesting that HAE can lead to anxiety and depression which in turn increase the frequency of attacks as in a vicious circle [15,23].

With the onset of the COVID-19 pandemic in Turkey, emotional changes were expected to occur in HAE patients considering their unawareness about the course of their disease and the effects of disease-related medications during the pandemic. Furthermore, some patients were possibly worried about having frequent attacks due to the presence of the infection and the possibility of experiencing difficulties in accessing to the hospital and drug supply. Therefore, we aimed to investigate the presence of psychological factors such as depression, stress, anxiety and fear related to the COVID-19 pandemic and related social restrictions, and their effects on disease activity in HAE patients by validated instruments.

Methods

Patients recruitment

This multicentre, exploratory study was conducted on adult patients with HAE Type I or Type II in the coordinating centre of the study, the adult immunology and allergy clinic at Istanbul Faculty of Medicine in Istanbul University and also in three other outpatient adult immunology and allergy clinics (KartalLütfiKırdar Education and Research Hospital, ŞişliEtfal Education and Research Hospital, CemilTaşçıoğlu City Hospital) in Istanbul in two different time periods outlined according to the degree of restriction measures applied by the government. The first period included the pandemic quarantine period (QP), the time period with strict restrictions beginning from 10th of March 2020 to the end of May 2020 and the first study assessments were completed in the last two weeks of May. The second period was 'the return to normal period' (RTNP) defined as the time period between the 1st of June 2020 and the end of August 2020 during which controlled social life was permitted [24]. The second study assessments were completed at the beginning of September. Patients older than 18 years of age with a confirmed diagnosis of C1-INH HAE according to the recent WAO/EAACI guideline for at least 6 months were included [25]. The patients who were not eligible for the study communication routes, those who did not give

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informed consent, those having severe HAE defined with severity scores of more than 30 for the last year, according to the HAE severity criteria defined as in Table Suppl. 1[26] those having more than 3 attacks in the last three months before the pandemic (BP) and those having psychiatric diagnosis and/or receiving psychiatric medications were excluded from the study.

Evaluation of HAE severity and mental health status

Demographic and baseline clinical data including frequency, localization and severity of HAE attacks before the pandemic period were retrospectively collected from the patient medical charts and the daily diaries that had been kept by the patients. During the first assessment in May, patients were evaluated with questionnaire forms questioning patients' experiences and opinions about COVID-19 during clinical visits and/or via online and/or phone call interviews (Table Suppl. 2). The number and localization of attacks assessed per 3-month period. Severity of HAE attacks were assessed with 10-point visual analogue scale (VAS10) [27]. Treatment options and long-term prophylaxis (LTP) was collected from the patient's medical charts and the daily diaries. Information about HAE attacks, LTP and attack treatments in the RTNP was re-evaluated via the same communication methods during the second assessment in September.

Psychological factors were appraised by the Turkish version of Depression Anxiety and Stress Scale 21 (DASS-21) which is a 4-point Likert scale, consisting of 21 items with three dimensions of 7 items for each scale with a rating system ("0"= Never, "1"= Sometimes, "2"= Frequently, "3"= Always) to measure depression, anxiety and stress, separately [28] (Table Suppl-2). Additionally, we used the Turkish version of Fear of COVID-19 scale (FC-19), a unidimensional 7-item, 5-point Likert scale with a rating system of "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree" [29]. The total score ranged from 7 to 35, meaning the higher the score the greater the fear of COVID-19 [29] (Table Suppl-2). Both DASS-21 and FC-19 scales were eligible for self-administration and did not require a psychiatrist for evaluation. Both scales were performed during the two assessment periods, comprising knowledge of previous three months.

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This study was approved by the Turkish MoH (2020-06-03T14_19_36). The institutional review board and the Ethics Committee of the coordinating centre approved the study (113239, 2020/ 78363)and informed consent was obtained from all study participants.

Statistical analysis

Statistical analysis was performed by SPSS.21 version. GraphPad Prism software was used for graphical analysis Categorical variables were summarized as frequencies and percentages. Continuous variables were given as mean values and standard deviations or median (min-max) values according to the distribution of the data. The Wilcoxon test was used for comparison of data that were not normally distributed. Mann- Whitney U test and Kruskal- Wallis test was conducted to evaluate the different groups. The relationship between the number of HAE attacks per 3-month period in QP and RTNP, severity and DASS-21, FC-19 scores were analysed by Spearmen's correlation test and multiple regression analysis. The two-sided p value <0.05 determined the statistical significance.

Results

Demographic and clinical findings of the study participants

A total of 140 patients were enrolled in the first assessment. One patient experiencing anosmia, cough and fever at the beginning of the study was considered as being infected by SARS-Cov-2 and excluded from the study since he did not complete the diagnostic tests of the infection and was not compliant to fill in the necessary study documents afterwards. None of the study participants were diagnosed as COVID-19 during the study period.

The demographic and clinical characteristics of 139 patients are listed in Table 1. 86.3% of patients (n=120) and 13.6% (n=19) had Type 1 and Type 2 C1-INH HAE, respectively. The median symptom duration was 24 years (min-max :0-63). LTP and attack treatments in QP and RTNP are shown in Table 1.

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Results of specific questions related to COVID-19 period

62.6% of patients (n=87) stated that they were afraid of having an attack during the pandemic and 31.6% (n=44) reported that they thought their disease was risky in terms of COVID-19. 77.7% (n=108) and 75.5% (n=105) were afraid of applying to the hospital and emergency rooms (ER)s for attack treatment during the pandemic, respectively.

In the QP, the application to ERs were slightly lower than those in RTNP while self-administration of icatibant was higher in QP than in RTNP as shown in Table 1. 23% (n=32) and 9 % (n=12) did not apply to the ERs despite the need of treatment in QP and RTNP, respectively.

49 patients were not working, 8 patients were retired and 17 were students before the pandemic. The employment and education conditions in QP and RTNP of the patients are shown in Table 1.

38.8% (n=54) and 7.9% (n=11) were on LTP; danazol and tranexamic acid, respectively which are the only available treatment options for LTP. During the pandemic, 33.8% (n=22) increased the doses of danazol/tranexamic acid, 55.3% (n=36) did not change the doses or the dose intervals of LTP, 10.7% (n=7) decreased their LTP usage and only one patient discontinued LTP. 38.4% (n=25) did not use 2 or more consecutive doses of danazol/tranexamic acid. During the QP, only one patient reported that she had problems to obtain LTP and 6.4% (n=9) had difficulties in obtaining pdC1-INH concentrate.

Evaluation of HAE attacks in QP and RTNP

The median number of HAE attacks and VAS severity scores are shown in Figure 1. The number of HAE attacks were higher in QP than RTNP and BP ($p=0.001$, $p<0.001$) respectively) while severity of attacks was similar among QP and RTNP ($p>0.05$) (Figure 1 A.B).

The attack sites of the patients during BP, QP and RTNP were similar in terms of distribution and their frequency as shown in Table 2.

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Results of mental health status measures in QP and RTNP

The frequencies of stress, anxiety, depression subscale analysis in QP and RTNP are shown in Table 3. In the QP, 139 patients were evaluated with DASS-21 assessments. The median scores of the subscales of stress, anxiety, depression and total DASS-21 items were 7 (min-max: 0-19), 3 (min-max: 0-18), 5 (min-max: 0-18), and 16 (min-max: 0-55), respectively. The mean of FC-19 scores in the QP was 23.5 ± 6.6 (Figure 2).

126 patients were re-evaluated in the RTNP with the same scales. The median scores of the subscales of stress, anxiety, depression and total DASS-21 items were 5 (min-max: 0-19), 2 (min-max: 0-18), 3 (min-max: 0-19), and 11 (min-max: 0-55), respectively and the mean of FC-19 scores in the RTNP was 18.3 ± 6.8 (Figure 2).

In comparison of the patients' psychological features in two periods, all three dimensions of DASS-21 scale (stress, anxiety, depression), DASS-21 total scores and FC-19 scores were higher in the QP than the RTNP ($p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively) (Figure 2).

Correlation analysis between clinical features and mental health status in QP and RTNP

Positive correlations between the number, severity of HAE attacks and DASS-21 anxiety, stress, depression, DASS-21 total scores, and FC-19 scores were observed in QP and RTNP (refer to Table 4 for each r, p values) (Table 4).

In the QP, DASS-stress ($p<0.001$), DASS-anxiety ($p<0.001$), DASS-depression ($p<0.001$), DASS-total ($p< 0.001$) and FC-19 [OR 3.00 (95% CI: 0.72- 5.28; $p=0.010$)] scores were higher in female patients Although we did not observe significant correlations between education level, age, BMI, three dimensions of DASS-21 scale in the QP, older ages indicated higher FC-19 scores [OR 0.106 (95% CI 0.03- 0.18; $p=0.007$)].

Similarly, DASS-stress ($p<0.001$), DASS-anxiety ($p<0.001$), DASS-depression ($p<0.001$), DASS- total ($p< 0.001$) and FC-19 scores [OR 4.04 (95% CI 1.56-6.52); $p=0.002$)] were higher in female patients in the RTNP. We did not observe significant correlations between education level, age, BMI, three dimensions of DASS-21 scale in the RTNP however we observed higher FC-19 scores in older patients [OR .10 (95% CI 0.01-0.18; $p=0.019$)].

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We did not observe significant differences in three dimensions of DASS-21, total DASS-21 scores, FC-19 scores, number and severity of HAE attacks among employed and unemployed patients and also among active/flexible working patients and on unpaid leave patients /fired ones in QP and RTNPs.

We observed higher number of attacks in those who were not receiving LTP (n=74 in QP, n=69 in RTNP) than those who were on LTP (n=65 in QP, n=57 in RTNP) in both periods (p=0.05 in QP, p=0.015 in RTNP). We did not observe significant differences between the groups receiving or not receiving LTP about attack severity, three dimensions of DASS-21, total DASS-21 and FC-19 scores.

Discussion

This novel study assesses for the first time the effects of psychological factors related to COVID-19 on HAE activity and severity. It indicates that psychological factors including anxiety, depression, stress and fear can negatively influence the activity of the disease in HAE patients and this effect can be higher during the application of strict social restrictions to reduce the transmission of the viral infection among populations.

In our study during the QP, the number and severity of HAE attacks increased in correlation with depression, anxiety, stress and fear related to COVID-19 which were determined with two validated tools, DASS-21 and FC- 19. Although there have been no reports regarding the influence of a pandemic on mental and physical health status of HAE patients so far, we believe the negative effects of COVID-19 on psychology and disease activity in HAE can be expected, considering the well-established role of psychologic stress as a common trigger of HAE attacks[12,23]. Furthermore, during the outbreak of the COVID-19 pandemic, widespread fear, anxiety, depression, adjustment disorders were seen not only in SARS-Cov2 infected patients but also in healthy individuals[30,31]. Although we have no data about the mental health status of our HAE patients before the pandemic, when we consider the effect of the pandemic on healthy subjects in general population, we can speculate that the pandemic has potentially increased anxiety, stress, depression and fear among our HAE patients. Besides, we did not include patients with known psychiatric disorders and/or those receiving such medications which may further

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strengthen our assumption. Otherwise, we believe it might have been hard to demonstrate differences in mental health status in the presence of psychiatric comorbidities. Also, by excluding patients with severe HAE from the study, we think that we have demonstrated the link between the deterioration in mental health status during the pandemic and HAE severity more accurately. We believe that the differences in attack severity could be hard to distinguish in patients who were already known to have experienced severe attacks.

Since the number of COVID-19 patients noticeably decreased in Turkey during the RTNP as a result of strict isolation measures in the QP, most social isolation rules were gradually loosened starting from the beginning of June as in most of the other countries. We observed a significant decrease in DASS-21 and FC-19 scores together with the decrease in the attack numbers in the RTNP. We can assume that this is a consequence of people getting used to living with the pandemic beside the loosened rules of quarantine in this period. All these factors might be important in decreasing the scores together with the number and severity of HAE attacks, however social restrictions must have played the major role on our results.

In the current study, depression, anxiety, stress and fear related to COVID-19 were higher in female patients, showing the psychiatric impact during the pandemic and that related social restrictions may influence women more than men. Previous studies indicated that anxiety and depressive disorders are more frequent in women and being a female has a negative effect on post-traumatic stress disorder symptoms during the COVID-19 pandemic [32]. Also female HAE patients suffer more frequent and severe angioedema attacks than males, especially in reproductive ages due to hormonal alterations, during pregnancy and delivery periods [33]. The fact that age can negatively affect anxiety, stress and depression is well observed in quality of life studies in chronic diseases [34]. However, we only observed higher FC-19 scores in older participants. Since it has been reported that patients older than 65 years of age are at risk for more severe COVID-19, it is acceptable to observe that older age has worse FC-19 scores. However, it might be speculative to make a conclusion in our study since only 5 patients were within this risky age group. Although BMI is another important issue that can be related to higher frequency of depression and anxiety in previous studies [35,36] and patients with higher BMI are more vulnerable to COVID-19 [37], we have not observed such a relation in our patients. Besides our study group consisted of a homogenous group of non-severe HAE patients according to their

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attacks in the last year. Moreover, both mental health status and HAE attack frequency changed during different restriction periods, despite the fact that same age, gender and BMI factors remained the same.

We did not observe significant differences in the frequency or severity of attacks, DASS-21 and FC-19 scores in the two periods among employed and unemployed patients, also among active/flexible working patients and unpaid leave patients /fired ones. The influence of changes in working conditions due to the pandemic on our results can be ignored since the majority of the working patients had more flexible or working from home opportunities and few were on unpaid leave or fired during the pandemic.

As expected, we observed higher number of attacks in patients without LTP compared to those receiving LTP. However, scales we used to determine mental health status revealed no difference among these groups. Since the majority of the patients were able to reach both attack medications and LTP during the pandemic, other factors seemed to be more important for disease severity in our patients.

In our study the majority of attack sites were the extremities, followed by the abdomen. In a previous study including pediatric population, mental stress-triggered attacks were mostly on abdomen [13]. This difference might depend on the fact that we did not include pediatric patients in our study.

As a limitation of this study, we could not evaluate the mental health status of our patients with the same validated tools prior to the study which restricted us from determining the clear effects of the pandemic over our study group. However as discussed earlier, we have assumed that this pandemic might have influenced our patients as it did to the healthy individuals in studies on the general population. During the study, we could not perform the initial severity score assessment method used for the inclusion of the participants since it necessitates over a 6-month period of follow up[38]. We could not perform specific angioedema severity (AAS, AECT)[39,40] and quality of life (AE-QoL, HAE-QoL)[41,42] assessment tools in our study since they either have not been validated in Turkish or validated but not published yet[43]. Although we believe VAS10 that is suitable for application during the pandemic is a quick, easy, self-administered method to assess severity of HAE. After this outbreak, we hopefully plan to perform the same psychiatric status measures, specific angioedema severity and quality of life

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assessment tools on our study group in order to see the accurate long-term effects of the pandemic.

In conclusion, our results showed that HAE patients can be mentally deteriorated by a pandemic despite not being infected and eventually their disease controls may be disrupted. Management of HAE should include multidisciplinary integration including medical, social, psychological interventions during crisis like a pandemic and telemedicine should become widespread for such vulnerable patient groups.

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Conflicts of interest

Authors state that there is no conflict of interest about this study.

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Figure legends

Figure 1. (A). Median number of attacks in BP, QP and RTNPs. Higher frequency of attacks was observed in QP. **(B).** The median VAS severity scores of HAE attacks in QP and RTNPs. There was no difference regarding the severity of HAE attacks.
Abbreviations: BP, before pandemic period; QP, quarantine period; RTNP, return to normal period; IQR, interquartile range; min, minimum; max, maximum; VAS, visual analogue scale

Figure 2. (A). Median scores of DASS-21 dimensions in QP and RTNPs. Three dimensions of DASS-21 and DASS-21 total scores were higher in QP than those in RTNP.
(B). Mean scores of Fear of COVID-19 (FC-19) scale in QP and RTNPs. FC-19 scores were higher in QP than those in RTNP. Abbreviations: QP, quarantine period; RTNP, return to normal period; IQR, interquartile range; SD, standard deviation.

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Table 1. Demographic and clinical features of the study group depending gender

	QP n=139		RTNP n=126	
	Female	Male	Female	Male
n	95	44	87	39
Age, years (mean ± SD)	38.5 (13.69)	38.07 (14.63)		
BMI <18.5	7	0	7	0
18.5-24.9	40	15	38	13
>25	48	29	42	26
Education (n)				
literate	2	1	2	1
Primary	39	8	36	8
High school	18	13	16	12
University	35	22	33	18

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Employment status (n)				
Employed	32	33	30	30
Active work	3	7	3	6
Flexible work	17	11	16	10
Salary without work	5	5	5	4
Unpaid leave	6	9	5	9
Fired	1	1	1	1
Unemployed	46	3	41	2
Retired	5	3	5	2
Student	12	5	11	5
Type 1 / Type 2 C1-INH-HAE (n)	82/13	38/6	75/12	35/4
LTP (n)				
Danazol	31	23	27	20
Tranexamic acid	8	3	7	3
None	56	18	53	16
Treatment of attacks (n)				
Pd C1-INH	26	10	28	14
Icatibant	45	21	41	15
Emergency room visits (n)	96	31	101	34

Abbreviations: BMI, body mass index; C1-INH-HAE, HAE with C1-inhibitor deficiency; LTP, long term prophylaxis; Pd C1-INH, Plasma derived C1 inhibitor concentrate; QP, quarantine period; RTNP, return to normal period; SD, standard deviation

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Table 2. Distributions and frequencies of HAE attack localizations during QP and RTNPs

	BP	QP	RTNP
Number of patients	n=139	n=139	n=126
Attack sites			
Extremities n, (%)	69 (49.6)	89 (64)	81 (64.2)
Abdomen n, (%)	48 (34.5)	72 (51.7)	67 (53.1)
Larynx n, (%)	8 (5.7)	21 (15.1)	18 (14.2)
Face n, (%)	10 (7.1)	18 (12.9)	19 (15)
Genitalia n, (%)	6 (4.3)	4 (2.8)	14 (11.1)
no attack n, (%)	25 (17.9)	22 (15.8)	21 (16.6)

Abbreviations: BP, before pandemic; QP, quarantine period; RTNP, return to normal period

Table 3. The frequencies of DASS subscale analysis in QP and RTNP

	QP	RTNP
	n=139	n=126
DASS- stress normal (%)	54	67.6
mild (%)	13.7	12.9
moderate (%)	22.3	5.8

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Severe (%)	8.6	1.4
very severe (%)	1.4	2.9
DASS-anxiety normal (%)	57.6	60.4
mild (%)	12.9	12.2
moderate (%)	10.8	7.9
severe (%)	8.6	5.8
very severe (%)	10.1	4.3
DASS- depression normal (%)	49.6	59.7
mild (%)	15.1	10.1
moderate (%)	27.3	15.1
severe (%)	4.3	2.2
very severe (%)	3.6	3.7

Abbreviations: DASS, depression anxiety stress scale; QP, quarantine period; RTNP, return to normal period

Table 4. The correlation analyses between psychological features and frequency and severity of HAE attacks

	Quarantine period				Return to normal period			
	Number of attacks		Severity of attacks		Number of attacks		Severity of attacks	
	r	p	r	p	r	p	r	p

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DASS-21 stress	.353	<0.001	.314	0.001	.422	<0.001	.455	<0.001
DASS- 21 anxiety	.286	0.001	.357	<0.001	.347	<0.001	.412	<0.001
DASS-21 depression	.279	0.001	.364	<0.001	.362	<0.001	.340	<0.001
DASS-21 total	.336	<0.001	.379	<0.001	.414	<0.001	.445	<0.001
Fear of COVID-19	.184	0.03	.230	0.013	.284	0.001	.395	<0.001

Abbreviations: DASS, depression anxiety stress scale

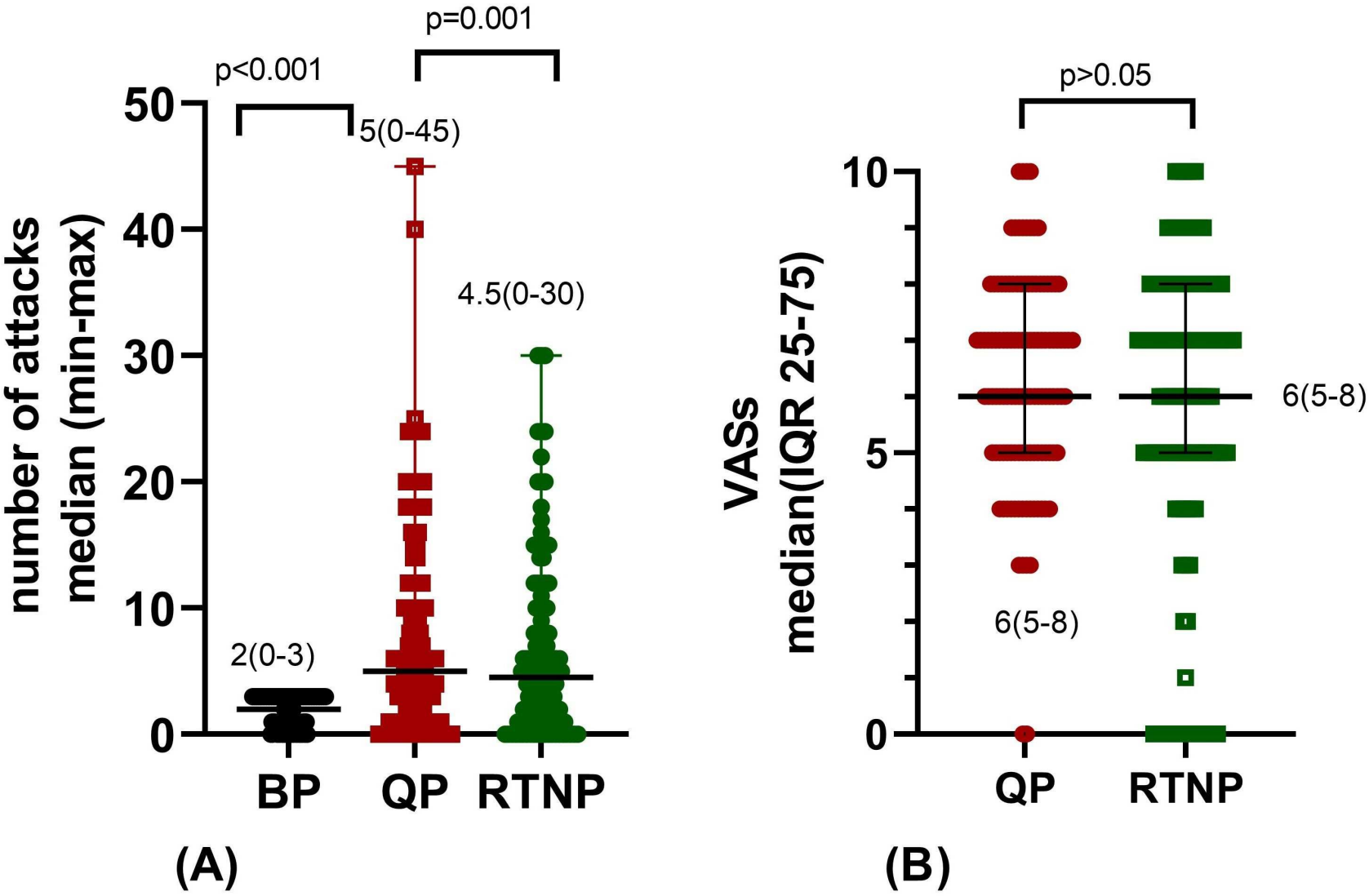
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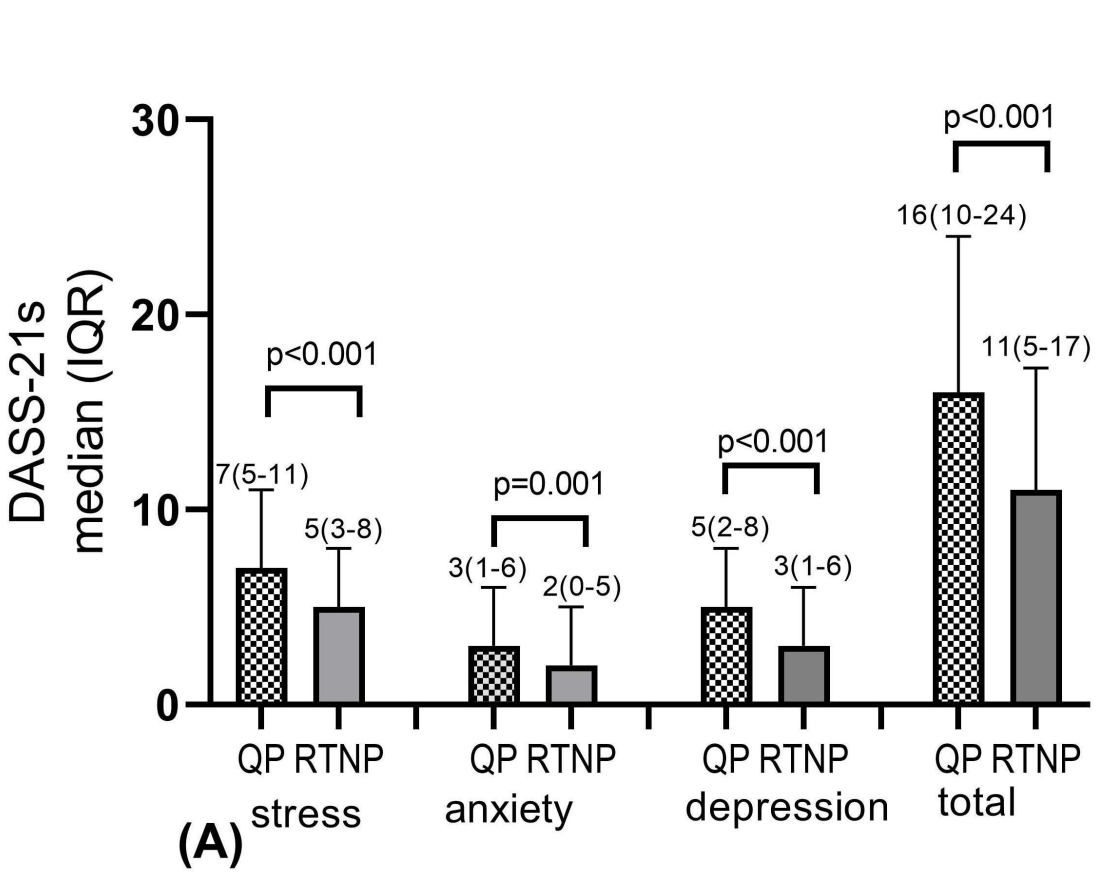
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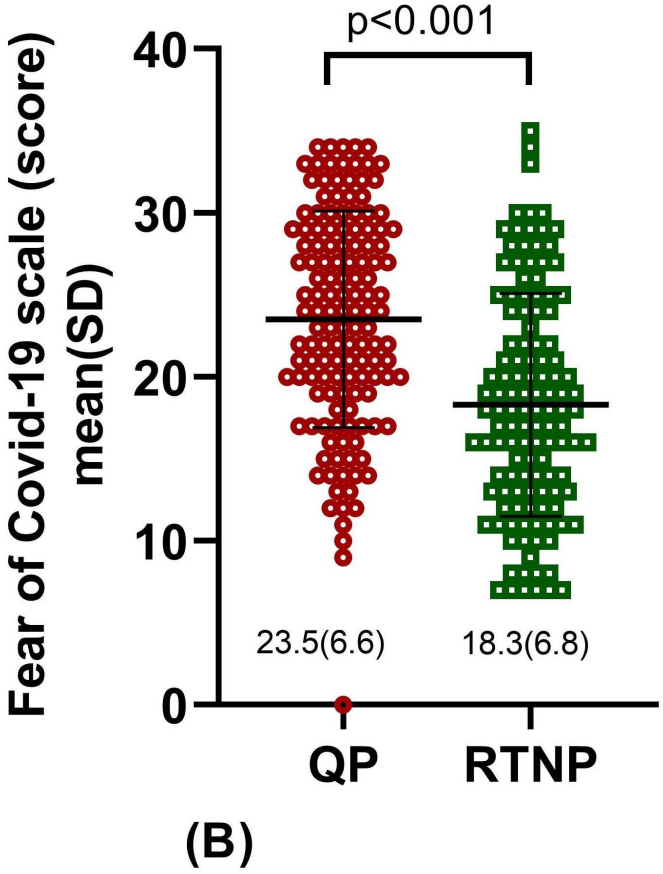
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