



The Impact of SARS-CoV-2 Transmission Fear and the COVID-19 Pandemic on the Mental Health of Patients with Primary Immunodeficiency Disorders and Severe Asthma, and Other High-Risk Groups

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ABSTRACT

Objective: The effect of the COVID-19 pandemic on mental health in the long term is unclear. We evaluated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-related transmission fear and mental-health disorders in populations at high risk for COVID-19.

Materials and Methods: Healthcare workers and patients with primary immunodeficiency disorders (PIDs), severe asthma, malignancy, cardiovascular disease, hypertension, and diabetes mellitus were included in the study. The hospital anxiety and depression scale (HADS) and Fear of Illness and Virus Evaluation (FIVE) scales were applied during face-to-face interviews.

Results: There was a total of 560 participants, 80 per group; 306 (55%) were female. The FIVE and HADS-A scale scores of health care workers were significantly higher than the other groups ($p = 0.001$ and 0.006). The second-highest scores were in patients with PID. There was no significant difference between the groups in HADS-D scores ($p = 0.07$). There was a significant positive correlation between FIVE scale scores and anxiety ($r = 0.828$; $p < 0.001$) and depression ($r = 0.660$; $p < 0.001$). The FIVE scale had significant discriminatory power for anxiety (AUC = 0.870, 95% confidence interval [CI] = 0.836–0.904; $p < 0.0001$) and depression (area under the curve = 0.760, 95% CI = 0.717–0.803; $p < 0.0001$).

Conclusion: During the COVID-19 pandemic, mental-health disorders may develop in patients with comorbidities, especially healthcare workers. They should be referred to mental-health centers.

Keywords: Asthma, COVID-19, fear of virus transmission, mental health, primary immunodeficiency

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease it causes, coronavirus disease-2019 (COVID-19), became a pandemic in 2020 (1). It

spread rapidly worldwide; there have been over 160 million confirmed cases and over 3 million deaths (2). The spectrum of symptomatic infection ranges from mild to fatal. Pneumonia is the most common serious infection,

characterized by fever, dry cough, dyspnea, and bilateral infiltrates on chest imaging (3, 4). Severe COVID-19 affects predominantly older patients and those with underlying comorbidities. Comorbidities associated with severe disease and mortality include primary or secondary immunodeficiency, pulmonary disease, cardiovascular disease, diabetes mellitus, hypertension, and malignancy (3, 5-7).

COVID-19 spreads via the respiratory tract among people in relatively close physical contact. The pandemic has caused anxiety, depression, and other psychological disorders (8). The immunocompetent mostly recover from COVID-19, but those with primary or secondary immunodeficiency may not. Patients with primary immunodeficiency, who have reduced health-related quality of life, will therefore need mental health support (9). Consideration of the psychological status of patients with chronic diseases at high risk for morbidity and mortality from COVID-19 is crucial. In this study, we compared COVID-19 transmission fear-induced anxiety and depression in patients with primary immunodeficiency disorders, those with other comorbidities, and healthcare workers at the front line of the COVID-19 pandemic. We evaluated the rates of mental health disorders in individuals at high risk of COVID-19-related morbidity and mortality.

MATERIALS and METHODS

Study Design

This was a descriptive, comparative, and cross-sectional study conducted at the Necmettin Erbakan University Meram Medical Faculty of Medicine Hospital, a large tertiary hospital. The study was approved by the local Ethics Committee of the Necmettin Erbakan University Meram Faculty of Medicine (decision no. 2020/2448). The study complied with all relevant tenets of the Declaration of Helsinki (1975). Healthcare professionals engaged in the response to the COVID-19 pandemic and patients with chronic diseases (primary immunodeficiency disorders, severe asthma, hypertension, diabetes mellitus, cardiovascular system diseases, and malignancies) were included in the study (Figure 1). Severe asthma is defined as uncontrolled despite adherence to the highest appropriate dose of medication or worsening when high doses of medication are reduced (10). The study began on April 20, and ended on May 15, 2020. Verbal informed consent was obtained from all participants. The Hospital Anxiety and Depression Scale (HADS) and Fear of Illness and Virus Evaluation (FIVE) scales were applied during face-to-face interviews.

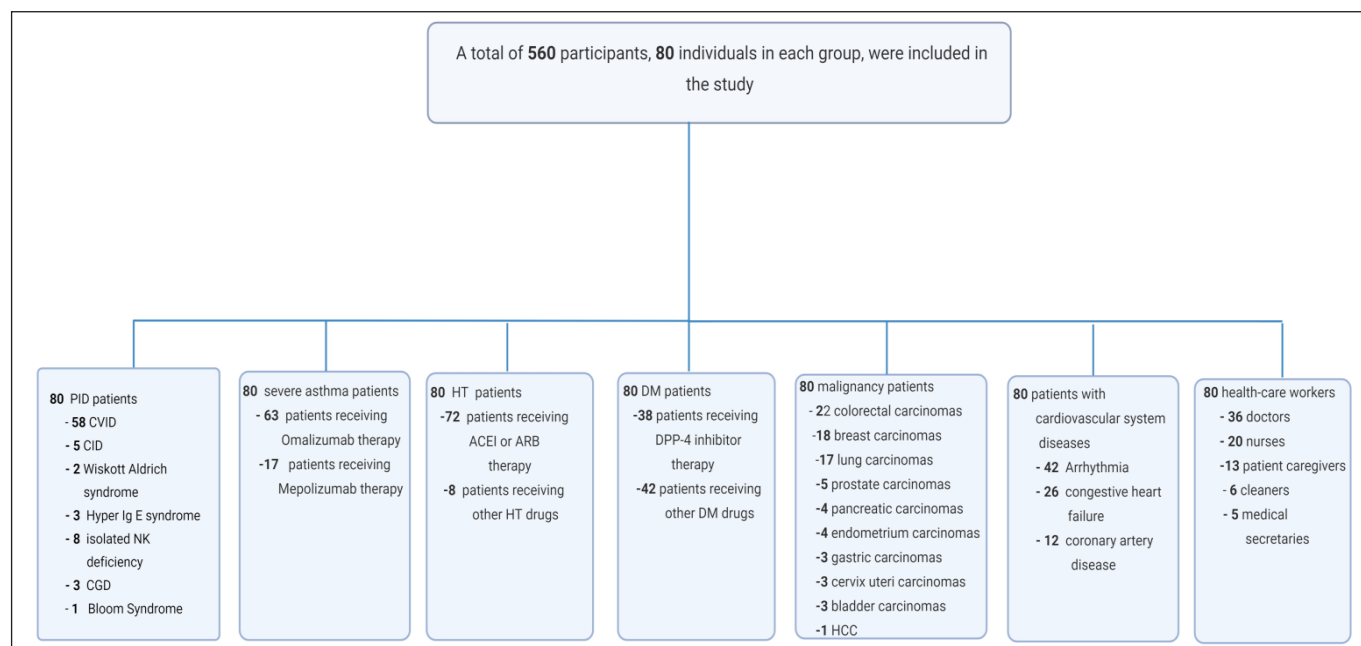


Figure 1. Flow chart of the study population.

ACEI: Angiotensin converting enzyme inhibitors, **ARB:** Angiotensin II receptor blockers, **CGD:** Chronic granulomatous disease, **CID:** Combined immunodeficiency, **CVID:** Common variable immunodeficiency, **DM:** Diabetes mellitus, **DPP-4:** Dipeptidyl peptidase-4, **HCC:** Hepatocellular carcinoma, **HT:** Hypertension, **IgE:** Immunoglobulin E, **NK:** Natural killer, **PID:** Primary immunodeficiency disorder.

Participants

The sample size was determined using the G*Power version 3.1 software. The minimum total sample size was calculated to be 287 (seven groups, 41 per group) subjects with 90% power at a 95% confidence interval with a two-tailed alpha of < 0.05 and a 0.25 effect size (f). A total of 560 participants, 80 per group, were included in the study (Figure 1).

Questionnaires

FIVE Scale

The FIVE scale was created by Prof. Dr. Jill Ehrenreich-May of Miami University (11) and was translated into Turkish and first used by Dr. Zekiye Çelikbaş of Gaziosmanpaşa University (12). The scale has adult, child, and parent forms; we used the adult form. The responses are scored on a 4-point Likert scale. The scale consists of four parts: Fears about contamination and illness (nine items, score 9–36), fears about social distancing (10 items, score 10–40), behaviors related to illness and virus fears (14 items, score 14–56 ranging), and impact of illness and virus fears (two items, score 2–8). There are a total of 35 items on the scale and the total score ranges from 35 to 140. Permission for use of the FIVE scale was obtained from those who prepared the original and the Turkish forms.

HAD Scale

The HAD scale was developed by Zigmond and Snaith (13), and is used to screen depression and anxiety in those with medical illnesses. The scale consists of 14 items; seven assessing anxiety and seven, depression. Responses are scored as 0–3 in quadruple Likert format. The lowest score is 0 and the highest is 21. Aydemir et al. reported that the Turkish version of the HADS is valid and reliable (Cronbach's α of 0.8525 and 0.7784 for the HAD anxiety and depression subscales, respectively). In the Turkish HADS, the cut-off scores for anxiety and depression were 10 and 7, respectively (14).

Statistical Analysis

Continuous variables are presented as means \pm standard deviation, and categorical variables as numbers and percentages. One-way ANOVA was used to evaluate continuous data, and the chi-squared test was used for categorical variables. The linearity of the relation between continuous variables was evaluated by Pearson (r) correla-

tion analysis. The receiver–operating characteristic (ROC) analysis was used to assess diagnostic performance. The cut-off points for the FIVE scale total and subscale scores were determined based on the Youden index by constructing a ROC curve. SPSS version 22.0 software (IBM Corp., Armonk, NY) was used for statistical analysis. The threshold for significance was $p < 0.05$.

RESULTS

Patients with PID, severe asthma, malignancy, CVS disease, HT, and DM, and healthcare workers were included in the study for a total of 560 participants (80 per group). There were 306 (55%) female and 254 (45%) male subjects. There was no significant difference in gender and age ($p = 0.08$ and 0.46) (Table I). Prior to the COVID-19 pandemic, the number of subjects who received professional support for their mental problem was highest in the healthcare workers group (28.75%, 23/80) ($p = 0.02$); this finding was replicated during the COVID-19 pandemic (11.25%, 9/80, $p = 0.4$) (Table I).

The healthcare workers group had the highest FIVE total (100.3 ± 20.5) and subscale scores ($p < 0.001$ for all), followed by the PID group for total score. (94.6 ± 13.6). The lowest score was in patients with hypertension (71.3 ± 19.3) (Table II).

The participants were evaluated in terms of anxiety and depression according to the cut-off values (10 points for HADS-A and 7 points for HADS-D) determined in the Turkish validation study of the HADS scale. The group with the highest proportion of participants with a HADS-A score higher than the cut-off value was that of the healthcare workers (51.2%, 41/80) ($p = 0.006$). There was no significant difference between the groups in the HADS-D score ($p = 0.07$) (Table II).

In the total population, there was a strong positive correlation between FIVE scale scores and anxiety ($r = 0.828$; $p < 0.001$), and Pearson correlation analysis showed a moderate positive correlation between the FIVE scale score and depression ($r = 0.660$; $p < 0.001$). For distinguishing between participants with and without anxiety, the cut-off total score was 96, with 79.1% sensitivity and 86.6% specificity. The FIVE scale had significant discriminatory power (area under the curve [AUC] = 0.870, $p < 0.0001$, 95% confidence interval [CI] = 0.836–0.904) (Table III and Figure 2).

Table I. Gender, age, and mental health.

		PID (n = 80)	Severe Asthma (n = 80)	Malignancy (n = 80)	CVS Disease (n = 80)	HT (n = 80)	DM (n = 80)	Healthcare Workers (n = 80)	p
Gender, n (%)	Female	44 (55)	55 (69)	36 (45)	41 (51)	45 (56)	39 (49)	46 (57)	0.08
	Male	36 (45)	25 (31)	44 (55)	39 (49)	35 (44)	41 (51)	34 (43)	
Age, year (mean ± SD)		38.9 ± 14.2	49.2 ± 13.8	53.6 ± 12.2	59.6 ± 9.6	54.7 ± 9.5	52.2 ± 10.7	36.5 ± 7.3	0.46
Were you diagnosed with a mental illness before the COVID-19 pandemic?	Yes/No	13/67	12/68	8/72	15/65	9/71	9/71	23/57	0.02
Did you need professional support for mental health problems during the COVID-19 pandemic?	Yes/No	6/74	2/78	5/75	6/74	5/75	3/77	9/71	0.4

PID: Primary immunodeficiency disorder; **CVS:** cardiovascular system; **HT:** hypertension, **DM:** diabetes mellitus; **COVID-19:** Coronavirus Disease 2019

Table II. HADS scores and FIVE scale scores.

		PID (n = 80)	Severe Asthma (n = 80)	Malignancy (n = 80)	CVS Disease (n = 80)	HT (n = 80)	DM (n = 80)	Healthcare workers (n = 80)	p
HADS-A Score, n (%)	Normal	44 (55)	52 (65)	52 (65)	55 (68.8)	61 (76.3)	56 (70)	39 (48.8)	0.006
	High	36 (45)	28 (35)	28 (35)	25 (31.2)	19 (23.7)	24 (30)	41 (51.2)	
HADS-D Score, n (%)	Normal	47 (58.8)	56 (70)	43 (53.8)	56 (70)	59 (73.8)	55 (68.8)	48 (60)	0.07
	High	33 (41.2)	24 (30)	37 (46.2)	24 (30)	21 (26.2)	25 (31.2)	32 (40)	
Fears about Contamination and Illness		25.2 ± 4	22.06 ± 5	23.2 ± 5.5	22.6 ± 5.8	18.8 ± 6.1	20.6 ± 6.3	25.3 ± 5.8	< 0.001
Fears about Social Distancing		24.9 ± 5.3	24.6 ± 6.5	24.4 ± 6.2	24.1 ± 6	20.8 ± 6.5	23.1 ± 7.1	27.4 ± 6.8	< 0.001
Behaviors Related to Illness and Virus Fears		39.1 ± 5.8	37.3 ± 5.7	39.7 ± 6	36.6 ± 6.1	32.2 ± 7	34.5 ± 6.4	41.8 ± 7.4	< 0.001
Impact of Illness and Virus Fears		5.3 ± 1.8	5.1 ± 1.6	5.2 ± 1.6	4.6 ± 1.6	3.8 ± 1.8	3.7 ± 1.5	5.9 ± 1.5	< 0.001
FIVE Scale Total Score		94.6 ± 13.6	89.2 ± 16.7	92.6 ± 15.9	87.8 ± 17.1	71.3 ± 19.3	81.9 ± 18.3	100.3 ± 20.5	< 0.001

PID: Primary immunodeficiency disorder, **CVS:** Cardiovascular system, **HT:** Hypertension, **DM:** Diabetes mellitus, **HADS:** Hospital Anxiety and Depression Scale, **HADS-A:** Hospital Anxiety and Depression Scale-Anxiety subscale, **HADS-D:** Hospital Anxiety and Depression Scale-Depression subscale, **FIVE Scale:** Fear of Illness and Virus Evaluation scale

The ability of the FIVE scales to distinguish between participants with and without depression was significant. The cut-off total score was 96, sensitivity was 62.8%, and specificity was 76.9% for distinguishing participants with and without depression (AUC = 0.760, p < 0.0001, 95% CI = 0.717–0.803) (Table IV and Figure 3).

DISCUSSION

We evaluated the ability of the FIVE scale to detect anxiety and depression due to fear of disease and virus transmission. The FIVE and HADS-A scale scores of health care workers involved in the response to the COVID-19

Table III. Ability of FIVE scale scores to predict COVID-19–related anxiety.

Variables	AUC (95% CI)	Cut-off	p	Sensitivity (%)	Specificity (%)
FIVE PART-1	0.833 (0.797–0.868)	24	< 0.001	78.6	76.6
FIVE PART-2	0.843 (0.808–0.878)	26	< 0.001	73.6	78.6
FIVE PART-3	0.795 (0.756–0.835)	40	< 0.001	71.1	79.4
FIVE PART-4	0.857 (0.824–0.889)	6	< 0.001	77.1	83.3
FIVE TOTAL	0.870 (0.836–0.904)	96	< 0.001	79.1	86.6

FIVE Scale: Fear of Illness and Virus Evaluation Scale, **COVID-19:** Coronavirus disease 2019, **ROC:** Receiver operating characteristic, **AUC:** Area under the curve, **CI:** Confidence interval

Table IV. Ability of FIVE scale scores to predict COVID-19–related depression.

Variables	AUC (95% CI)	Cut-off	p	Sensitivity (%)	Specificity (%)
FIVE PART-1	0.737 (0.693–0.781)	24	< 0.001	67.3	69.8
FIVE PART-2	0.748 (0.704–0.791)	26	< 0.001	64.8	73.1
FIVE PART-3	0.705 (0.658–0.751)	40	< 0.001	60.7	73.1
FIVE PART-4	0.780 (0.739–0.821)	6	< 0.001	68.9	78.0
FIVE TOTAL	0.760 (0.717–0.803)	96	< 0.001	62.8	76.9

FIVE scale: Fear of Illness and Virus Evaluation scale, **COVID-19:** Coronavirus disease 2019, **ROC:** Receiver operating characteristic, **AUC:** Area under the curve, **CI:** Confidence interval

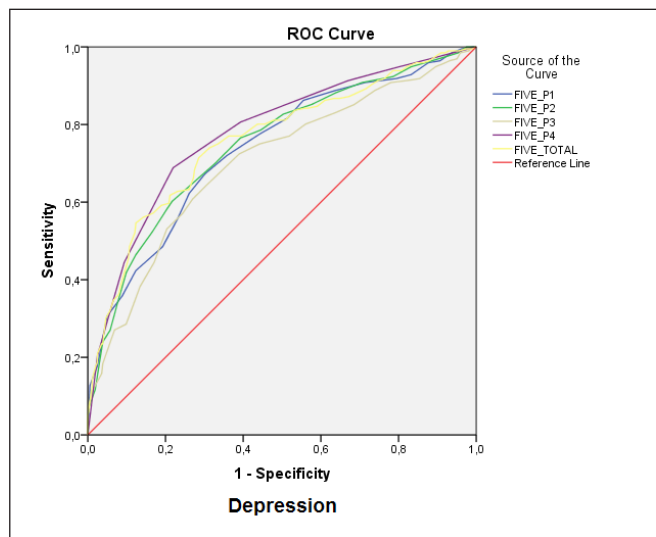


Figure 2. ROC analysis of FIVE scale total and subscale scores at baseline. FIVE scale total and subscale scores were set to a positive influence, and specificity and sensitivity were plotted.

ROC: Receiver operating characteristic, **FIVE:** Fear of Illness and Virus Evaluation, **FIVE P1:** FIVE Part-1 (fears about contamination and illness), **FIVE P2:** FIVE Part-2 (fears about social distancing), **FIVE P3:** FIVE Part-3 (behaviors related to illness and virus fears), **FIVE P4:** FIVE Part-4 (impact of illness and virus fears), **FIVE TOTAL:** Fear of Illness and Virus Evaluation scale total score.

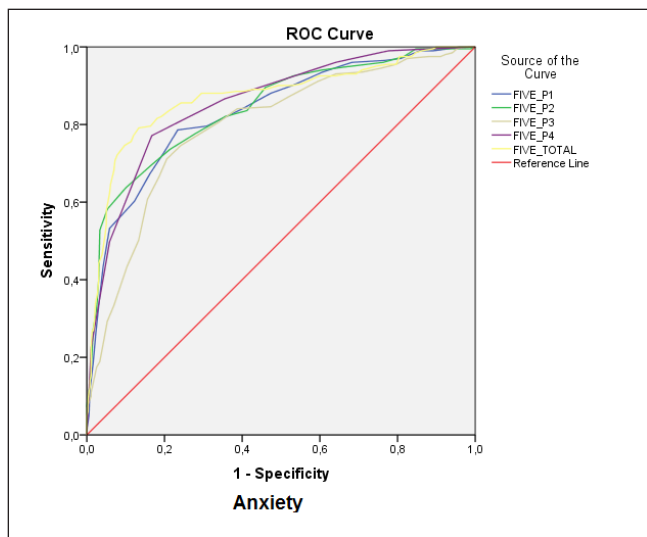


Figure 3. ROC analysis of FIVE scale total and subscale scores at baseline for depression. Notes: FIVE scale total and subscale scores were set to a positive influence, and specificity and sensitivity were plotted.

ROC: Receiver operating characteristic, **FIVE:** Fear of Illness and Virus Evaluation, **FIVE P1:** FIVE Part-1 (fears about contamination and illness), **FIVE P2:** FIVE Part-2 (fears about social distancing), **FIVE P3:** FIVE Part-3 (behaviors related to illness and virus fears), **FIVE P4:** FIVE Part-4 (impact of illness and virus fears), **FIVE TOTAL:** Fear of Illness and Virus Evaluation scale total score.

pandemic were significantly higher than those of patients with primary immunodeficiency (who had the second-highest scores) and other comorbidities. There was no significant difference between the groups in HADS-D scores.

Primary immune deficiency disorders are a group of more than 400 congenital immune defects (15). Some defects affect basic immunological pathways and induce susceptibility to common and opportunistic pathogens, resulting in recurrent or chronic infections (16). Children with primary immunodeficiency have a higher rate of mental health disorders than children with chronic diseases such as severe asthma and chronic renal disease (17). Such mental health disorders include depression, anxiety, somatization, social withdrawal, and decreased social skills. In addition, 18% of patients with pediatric-onset COVID have depression, which is associated with mortality, especially in patients with delayed diagnosis (18). Patients with primary immunodeficiencies are more vulnerable to SARS-CoV-2 and COVID-19, similar to other infectious agents, as compared to immune-competent individuals (9). Therefore, the COVID-19 pandemic impacts health-related quality of life and the risk of anxiety/depression in patients with PID, who have significantly higher rates of anxiety and depression than do the healthy population. Mental disorders contribute to PID morbidity and mortality (18). To improve the quality of life of these patients, timely referral and treatment are essential (19).

Stress might increase the risk of asthma and asthma-related morbidity by affecting the immune system (20). Although there is insufficient evidence that asthma is a risk factor for COVID-19, poorly controlled asthma can lead to a more complicated disease course (21, 22). However, the most common comorbidities among young patients hospitalized for COVID-19 are asthma, diabetes, and obesity (23). Because the effect of asthma on COVID-19 prognosis is uncertain, anxiety remains high. About 80% of asthma exacerbations are associated with viral infections. In allergic asthmatic patients, allergic sensitization and eosinophilic inflammation can disrupt the integrity of the airway epithelium, thereby paving the way for limiting the ability of virus clearance and fostering the location of viruses in the lower respiratory tract. Therefore, biologic agents, such as omalizumab (an anti-IgE antibody) and mepolizumab (a monoclonal antibody to IL-5), used in the treatment of severe allergic or eosinophilic asthma, may improve the prognosis of COVID-19 (24, 25). This would decrease the risk of COVID-19-related anxiety because

virus-induced asthma exacerbations will decrease. Our results support this hypothesis.

The higher FIVE scale scores and HADS-A scores of healthcare workers indicate the existence of pandemic-specific problems. Healthcare workers have a significantly increased risk of COVID-19 and other emerging infectious diseases compared to the general population (26). A major cause of distress in healthcare workers is fear of infection with SARS-CoV-2 and spreading it to their families (27). The pandemic requires isolation from families, depriving them of family support. Changes in the workplace and increases in working hours and workload also negatively affect the mental health of healthcare workers. In addition, social stigmatization and exclusion behaviors toward healthcare workers, whom the public consider to be most exposed to the virus, contribute to mental stress (28). The increase in the number of cases and mortality rates, as well as witnessing critical illness and death among their colleagues, exacerbate the issue (29). The shortage of personal protective equipment (PPE) and other materials increases anxiety about transmission (30).

In a recent study from Wuhan, China, severe symptoms, need for mechanical ventilation, and risk of death was higher in patients with COVID-19 and malignancy compared to those COVID-19 patients without malignancy (6). Psychiatric disorders such as major depression are more common in patients with malignancy compared to the general population (31). Depression is often accompanied by anxiety in these patients (32). It is crucial to support patients with malignancy to improve their quality of life and prevent the adverse psychological effects of the COVID-19 pandemic (33).

Patients with diabetes mellitus, cardiovascular disease, and hypertension have increased risks of severe disease and mortality for COVID-19 (34-36). The SARS-CoV-2 spike protein binds directly to the cell surface ACE2 receptor, facilitating viral entry and replication (37). Therefore, renin-angiotensin system inhibitors may increase ACE2 levels and so adversely affect the prognosis of COVID-19. There are similar speculations related to DPP-4 inhibitor drugs in patients with diabetes mellitus and COVID-19 (38). We evaluated the mental health of patients at high risk for COVID-19, and patients with hypertension had the lowest scores. However, only one quarter of patients who need psychological support are receiving treatment.

The focus is on drug and vaccine discovery for the eradication of COVID-19, and the mental health status of healthcare professionals, patients with primary immunodeficiency, and those with asthma and other comorbidities is being ignored. Authorities and clinicians should provide support and take precautions in this regard.

This study has several limitations. First, only a portion of the participants had diagnoses by mental health professionals. Patients with mental health disorders were referred to the psychiatry clinic. However, feedback was not received because of the pandemic. Second, the study was performed during the pandemic in a hospital setting by face-to-face interviews, and it was not compared with the mental health of a control group, without comorbidity, from the general population. Finally, face-to-face interviews in hospital settings may impact individuals' mental health during the pandemic.

Despite these limitations, this is, to our knowledge, the first comparison of fear of infection transmission-related anxiety and depression in adults with primary immunodeficiency and other high-risk patients. Our findings will facilitate determination of the anxiety and depression levels of patients with primary immunodeficiency, thus improving their quality of life.

In conclusion, during the pandemic, mental health disorders may develop in patients with comorbidities, especially healthcare workers. They should be referred to mental-health centers. Also, the authorities should take precautions to prevent healthcare services from being interrupted and prevent damage to the general population's mental health.

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