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Factors associated with progression of depression, anxiety, and stress-related symptoms in outpatients and inpatients with COVID-19: A longitudinal study

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Abstract

It is known that there is an increase in the frequency of psychiatric disturbances in the acute and post-illness phase of coronavirus disease (COVID-19). Comorbid psychiatric symptoms complicate the management of patients and negatively affect the prognosis, but there is no clear evidence of their progress. We aimed to determine psychiatric comorbidity in inpatients and outpatients with COVID-19 and recognize the factors that predict psychiatric comorbidity. For this purpose, we evaluated patients on the first admission and after 4 weeks. We investigated psychiatric symptoms in outpatients ($n = 106$) and inpatients ($n = 128$) diagnosed with COVID-19. In the first 7 days after diagnosis (first phase), sociodemographic and clinic data were collected, a symptom checklist was constructed, and the Hospital Anxiety and Depression Scale (HADS) and the Severity of Acute Stress Symptoms Scale (SASSS) were applied. After 30–35 days following the diagnosis, the SASSS and the HADS were repeated. In the first phase, the frequency of depression and anxiety were 55% and 20% in inpatients, and 39% and 18% in outpatients, respectively. In the second phase, depression scores are significantly decreased in both groups whereas anxiety scores were decreased only in inpatients. The frequencies of patients reporting sleep and attention problems, irritability, and suicide ideas decreased after 1 month. Patients with loss of smell and taste exhibit higher anxiety and depression scores in both stages. Our results revealed that the rate of psychiatric symptoms in COVID-19 patients improves within 1 month. Inpatients have a more significant decrease in both depression and anxiety frequency than do outpatients. The main factor affecting anxiety and depression was the treatment modality. Considering that all patients who were hospitalized were discharged at the end of the first month, this difference may be due to the elimination of the stress caused by hospitalization.

KEYWORDS
anxiety, COVID-19, depression, mental health, psychopathology

INTRODUCTION

The psychological effects of coronavirus disease (COVID-19), which causes extraordinary manifestations in various parts of the body, have drawn considerable attention (Bao et al., 2020; Hao et al., 2020; Huang & Zhao, 2020). There are several hypotheses regarding neuropsychiatric involvement in COVID-19. The first of these is the psychological standpoint, in which COVID-19 can cause anger, fear, anxiety, and other psychological disturbances in people with acute infection. It has been reported that these patients experience physical discomfort, loneliness, sensitivity, severe symptoms, and psychosocial stressors (Brooks et al., 2020; Hao et al., 2020). These stressors also can reduce immunity by altering the cell-mediated immune response, and this may play a role in the etiopathogenesis of depression (Osimo et al., 2020). Hao et al. (2020) reported that themes of shock, fear, hopelessness, boredom, and discrimination were prominent in interviews

with hospitalized patients (Hao et al., 2020). Another hypothesis was related to neurotrophic involvement (Wu et al., 2020).

The number of studies investigating the psychological effects of COVID-19 is still scarce (Mazza et al., 2020; Poyraz et al., 2021). Whereas insomnia, depression, and anxiety have been reported most frequently in acute periods in inpatients (Deng et al., 2020; Rogers et al., 2020), high rates of anxiety and depression were found in outpatients as well (Zarghami et al., 2020). Studies on the post-illness period have always been conducted in hospitalized patients. Mazza et al. (2020) evaluated COVID-19 survivors 1 month after hospital treatment and found depression in 31%, anxiety in 42%, and insomnia in 40% of the patients; they also reported that 56% of the patients scored in the pathological range in at least one clinical dimension (Mazza et al., 2020). In two similar studies, high rates of anxiety and depression were observed (Liu et al., 2020; Tomasoni et al., 2021). Poyraz et al. (2021) conducted an online survey approximately 50 days after discharge and found that 34% of patients had symptoms of clinically significant posttraumatic stress disorder, anxiety, and depression and reported an increased risk of suicide (Poyraz et al., 2021). These studies do not include any data related to psychiatric symptoms at the start of the disease. In addition, there has been no study comparing outpatients and inpatients. Considering that most patients undergoing treatment are isolated at home, the presence of and change in psychiatric symptoms are also of great importance for public health.

Only one study has monitored how the psychiatric effects in the acute phase of the disease progress in the following months. In that study, hospitalized patients were followed up for 6 weeks, and the relationship between anxiety and depression levels with loss of smell and taste was evaluated (Speth et al., 2020). There has been no study on the follow-up of outpatients. A recently published meta-analysis comparing acute and follow-up phases of COVID-19 patients has revealed that the severity of psychiatric symptoms decreases over a follow-up period (Xi et al., 2021), but comorbid mental problems complicate the management of the patient and negatively affect their prognosis (Turan et al., 2021; Xie et al., 2021). This may indicate the importance of detecting the risky ones in terms of mental health and early intervention in these patients. In this study, we aimed to determine psychiatric comorbidity in inpatients and outpatients with COVID-19, reevaluate these patients after 4 weeks, and identify the factors that predict psychiatric comorbidity by addressing aspects neglected in the studies mentioned earlier. We thought that examining the underlying physiological and psychosocial mechanisms associated with COVID-19 infection and observing the changes in symptoms in the process may also facilitate our understanding of the psychiatric symptom burden that develops due to the disease. We hypothesized that inpatients have more severe psychiatric symptoms than do outpatients, but recover better.

METHOD

Inpatients and outpatients who were diagnosed with COVID-19 at the Ankara University Ibni Sina Hospital and Başkent University Ankara Hospital between October 5, 2020, and November 30, 2020, were between the ages of 18 and 70 years, had clinically mild and moderate disease (Feng et al., 2020), did not need intensive care, did not have a history of a cognitive disorder, and who agreed to participate were included in the study. Of the 1,435 patients diagnosed with COVID-19 at the aforementioned hospitals between those dates, 322 met the inclusion criteria. However, 73 patients withdrew their consent, and 15 patients were not included in the analysis because they filled the scales incompletely. Of the remaining 234 patients, 128 were inpatients (hospitalized), and 106 were outpatients (managed at home in isolation). The study received approval from the Başkent University Ethics Committee (Ref. KA20/178), and written and oral consent were obtained from all participants. They were notified in advance that they would be contacted again after 1 month to answer questions regarding their condition.

Measurement instruments

Depression and anxiety levels were evaluated using the Hospital Anxiety and Depression Scale (HADS). This scale was developed by Zigmond and Snaith in 1983 whereas its Turkish reliability and validity study was conducted by Aydemir et al. (1997). We used HADS because it is a suitable tool for measuring the severity of anxiety and depression symptoms in nonpsychiatric patient populations (Norton et al., 2013; Zigmond & Snaith, 1983). Cronbach's α coefficient is .85 for the Anxiety subscale and .77 for the Depression subscale. HADS is a 4-point Likert-type self-reporting scale of 0 (minimum value it can be as it can be taken for duration, severity, etc.) to 3 (maximum value it can be as it can be taken for duration, severity, etc.) and consists of 14 questions. The total score ranges from 0–21, with a cutoff point of >7 for depression (HADS-D) and >10 for anxiety (HADS-A) in the Turkish version (Aydemir et al., 1997).

The Turkish form of the Severity of Acute Stress Symptoms Scale (SASSS) was developed by Ascibasi et al. (2017) based on the *Diagnostic and Statistical Manual of Mental Disorders DSM-V* diagnostic criteria for acute stress disorder. The 5-point Likert-type scale consists of seven items. Patients can score between 0 (never) and 4 (most of the time, severe); a score of 1 and above indicates that they have acute stress symptoms. Cronbach's α coefficient is .95 (Ascibasi et al., 2017).

Procedure

First evaluation

Because the first diagnosis and examinations are done within the first 7 days of hospitalization, we decided to complete our first measurement within 7 days. We thought that measurement within 3–7 days would be suitable to evaluate acute stress. Patients who agreed to be study participants completed a sociodemographic data form, a checklist, and self-assessment

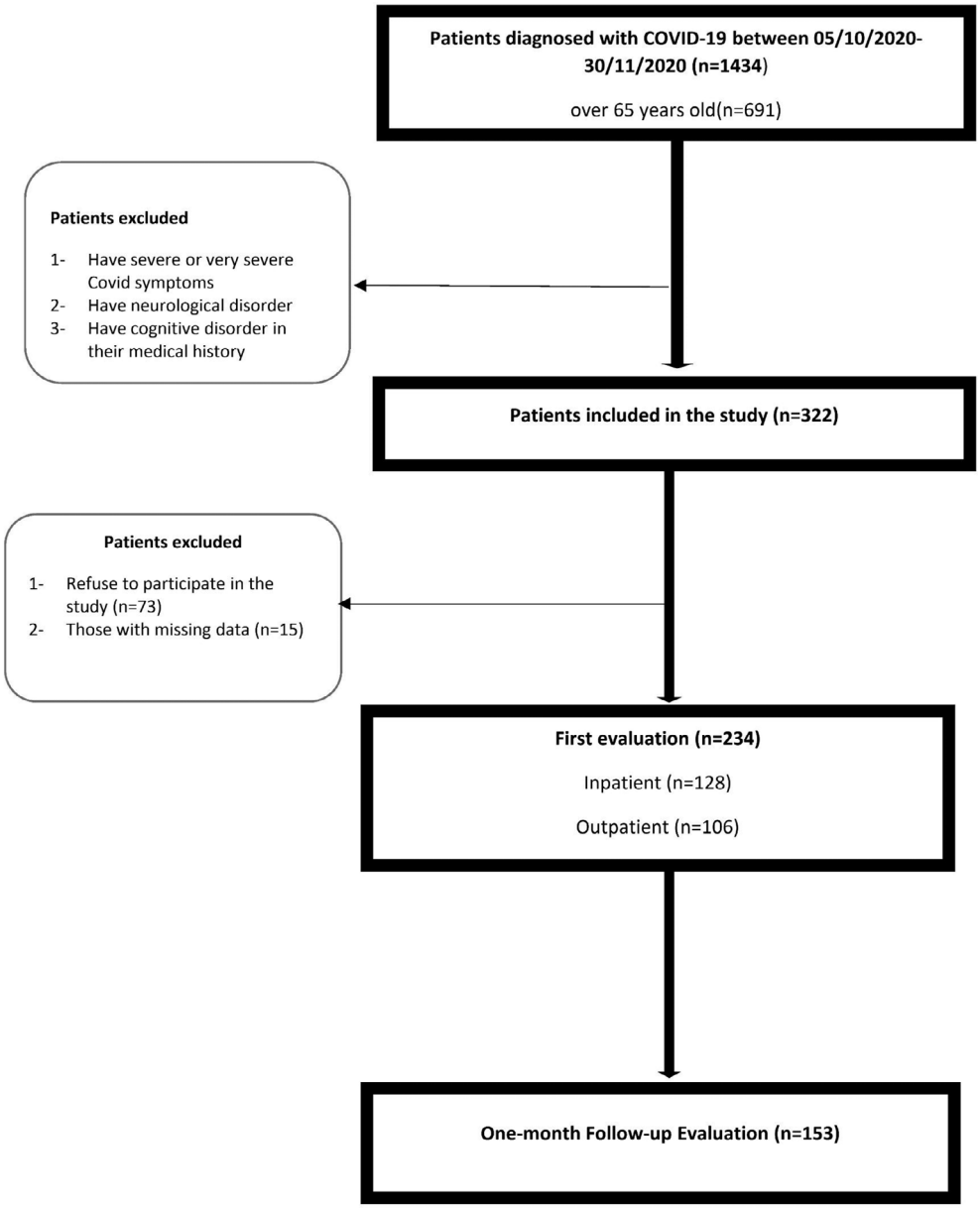

FIGURE 1 Flowchart of the participants in the study

scales. All participants were Turkish, and the sociodemographic data form and scales were written in Turkish. Inpatients filled out the self-assessment scales during hospitalization, and the scales were sent to the outpatients in the form of a link to a Google form because they were isolated at home after their diagnosis. Complete blood count, thoracic computerized tomography findings, and other clinical variables of the patients hospitalized during this period were noted (by the authors, D.O., G.Ç., J.H., E.G., İ.A.K.). Sociodemographic and clinical data forms were filled out by the patients, and clinical and laboratory findings, which are related to inflammation such as white blood cells (WBC), neutrophil, lymphocyte, neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), C-reactive protein (CRP), D-dimer, and also thoracic computerized tomography, were utilized together with the sociodemographic characteristics of the patients to constitute our data. A checklist consisting of frequently reported symptoms in previous studies, such as sleep problems, loss of taste and smell, visual and auditory hallucinations, self-harm, suicidal ideation, and attention deficit, was used with 15 patients as a preliminary study. These 15 patients were not included in the study or the analysis. The HADS and the SASSS were also used.

Follow-up evaluation

Patients who participated in the first part of the study were called on Days 30–35 after diagnosis to participate in the second part of the study. This second evaluation took place in the first month to see the subacute effects of stress. The checklist and HADS-D were used again. The flowchart in Figure 1 demonstrates the research procedure.

Statistical analysis

Data obtained from the study were analyzed using SPSS Version 17 (IBM, Armonk, NY, USA). The normality distribution was assessed using the Kolmogorov–Smirnov test and descriptive methods. Categorical variables were expressed as a percentage, numerical variables with normal distribution as mean and *SD*, and numerical variables without normal distribution as *Mdn* and interquartile range (IQR). The chi-square test was used for the comparison of categorical variables. For the comparison of independent groups, the *t* test was used for variables with normal distribution, and the Mann–Whitney *U* test was used for variables without normal distribution. For before–after comparisons, the McNemar test was used for categorical data, and the Wilcoxon test was used for continuous data. We used a repeated measure analysis of variance (rmANOVA), in which the anxiety and depression levels of the patients at hospitalization and discharge were handled separately as dependent variables. Gender, presence of pneumonia, history of psychiatric disease, and loss of smell and taste were determined as independent variables. The smell and taste losses of the patients were handled separately at the time of hospitalization and after discharge. Thus, a 2 × 2 status matrix emerged:

Condition 1: No loss at admission and no loss at the 1-month follow-up.

Condition 2: Loss at admission, but no loss at 1-month follow-up.

Condition 3: No loss at admission, but a loss at 1-month follow-up.

Condition 4: Loss at admission and the 1-month follow-up.As a result, a 2 × 2 × 2 × 2 × 2 × 4 × 4 patterned ANOVA was used as a whole for measurement time (first evaluation/1 month evaluation), gender (female/male), treatment modality (inpatient/outpatient), pneumonia (presence/absence), psychiatric disease history (yes/no), loss of smell (condition defined earlier), and loss of taste (condition defined earlier). Age and education status were put into ANOVA as covariates. *P* values <.05 were considered statistically significant.

RESULTS

Demographic and clinical characteristics of participants

Demographic and clinical characteristics and laboratory findings (CRP, WBC, neutrophil count, lymphocyte count, NLR, PLR, ferritin, D-dimer, CKMB, troponin) of the patients who participated in the initial and follow-up phases of the study are presented in Table 1. A total of 234 patients diagnosed with COVID-19 were included in the study. In total, 55% of the patients were inpatients, 56.4% were women, 53.8% were university graduates, and 66.2% were married. Furthermore, 65% of the 234 patients included in the study also participated in the follow-up phase of the study. Further analyses were performed only on those who participated in both phases.

In terms of sociodemographic and clinical characteristics, there was no difference between those who participated in only the first step of the study and those who participated in both steps. A comparison of those who attended only the first evaluation and those who participated in both evaluations is shown in Supplement 1.

TABLE 1 Demographic and clinical characteristics and laboratory findings of the study participants

Characteristic	Total participants ($N = 234$) *n* (%)	Patients who participated in follow-up ($n = 153$) *n* (%)
Gender/female	132 (56.4)	87 (56.9)
Age (years), *Mdn* (IQR)	41 (23)	39 (22)
Education (years) *Mdn* (IQR)	16 (8)	16 (4)
Marital status/married	155 (66.2)	97 (63.4)
Children/yes	157 (67.1)	95 (62.1)
Employment status/employed	136 (58.1)	94 (61.4)
Household size ($M \pm SD$)	2.96 ± 1.03	2.9 ± 1.07
Monthly income, Tl *Mdn* (IQR)	3500 (3400)	3500 (3750)
Chronic illness	57 (24.4)	37 (24.2)
History of psychiatric admission	54 (23.1)	38 (24.8)
Currently uses psychotropic medication	24 (10.3)	15 (9.8)
WBC (μl) *Mdn* (IQR)	5,670 (2715)	5,760 (2735)
Neutrophil (μl) *Mdn* (IQR)	3,335 (2252.5)	3,295 (2570)
Lymphocyte (μl) *Mdn* (IQR)	1,615 (877.5)	1,680 (862.5)
Platelet (μl) *Mdn* (IQR)	210,000 (107,000)	208,000 (104,000)
NLR *Mdn* (IQR)	1.89 (1.82)	1.72 (1.75)
PLR *Mdn* (IQR)	128.6 (89.73)	121.2 (83.52)
Ferritin (μg/L) *Mdn* (IQR)	133.0 (226.0)	125.7 (192.8)
CRP (mg/L) *Mdn* (IQR)	9.1 (43.5)	7.05 (35.2)
CKMB (μg/L) *Mdn* (IQR)	1.91 (25.5)	1.56 (6.95)
Troponin (ng/L) *Mdn* (IQR)	3.0 (5.41)	2.0 (4.81)
D-dimer (mg/L) *Mdn* (IQR)	23.0 (181.26)	1.35 (190.04)

Note: The employed group consists of freelance and paid employees; the unemployed group consists of housewives, retirees, students, and the unemployed. Chronic illnesses include hypertension, diabetes mellitus, and hypothyroidism.
Abbreviations: CKMB, creatine kinase-myoglobine binding; CRP, C-reactive protein; IQR, interquartile range; NLR, neutrophil-lymphocyte ratio; PLR, platelet–lymphocyte ratio; WBC, white blood cell.

Comparisons and correlations of demographic and clinical characteristics of inpatient and outpatient groups

Patients were treated in the hospital (inpatient) or managed at home (outpatient), depending on the severity of their

TABLE 2 Distribution of sociodemographic and clinical characteristics and laboratory findings of outpatients and inpatients

Characteristics	Outpatients *n* (%) or *Mdn* (Iqr)	Inpatients *n* (%) or *Mdn* (Iqr)	χ^2/p ($n = 153$)
Age	36.5 (18)	48 (29.5)	$Z = -5.016$[a] **$p < .001$**
Gender/female	69 (65.1)	63 (49.2)	$\chi^2 = 5.493$[b] **$p = .015$**
Years of education	16 (4)	12 (11)	$Z = -3.711$[a] **$p < .001$**
Marital status/married	65 (61.3)	90 (70.3)	$\chi^2 = 2.308$[b] $p = .315$
Employed	77 (72.6)	59 (46.1)	$\chi^2 = 16.789$[b] **$p < .001$**
Has history of psychiatric admission	32 (30.2)	22 (17.2)	$\chi^2 = 5.521$[b] **$p = .019$**
Currently using psychotropic medication	13 (12.7)	11 (8.6)	$\chi^2 = 0.849$[b] $p = .357$
Sleep disorder	61 (68.5)	23 (35.9)	$\chi^2 = 15.981$[b] **$p < .001$**
Loss of smell	62 (69.7)	38 (59.4)	$\chi^2 = 1.740$[b] $p = .187$
Loss of taste	55 (61.8)	37 (57.8)	$\chi^2 = 0.247$[b] $p = .619$
Attention deficit	29 (32.6)	17 (26.6)	$\chi^2 = 0.642$[b] $p = .423$
Irritability	28 (35.9)	16 (25.0)	$\chi^2 = 0.758$[b] $p = .384$
Forgetfulness	27 (30.3)	14 (21.9)	$\chi^2 = 1.359$[b] $p = .244$
Thoughts that life is not worth living/yes	19 (17.9)	11 (8.6)	$\chi^2 = 4.517$[b] **$p = .034$**
Desire to die/yes	11 (10.4)	10 (7.8)	$\chi^2 = 0.467$[b] $p = .494$
Plan to die/yes	3 (2.8)	2 (1.6)	$\chi^2 = 0.446$[c] $p = .661$
Neutrophil (μl)	3,295 (2150)	3,380 (2305)	$Z = -0.069$[a] $p = .945$
Lymphocyte (μl)	1,605 (907.5)	1,615 (877.5)	$Z = -0.008$[a] $p = .994$
NLR	1.79 (2.24)	1.90 (1.65)	$Z = -0.131$[a] $p = .896$
PLR	152.1 (86.9)	122.0 (85.5)	$Z = -1.102$[a] $p = .270$
Ferritin (μg/L)	85.0 (161.0)	164.8 (274.4)	$Z = -2.184$[a] **$p = .029$**
CRP (mg/L)	5.85 (6.83)	12.25 (70.83)	$Z = -2.164$[a] **$p = .030$**
CK-MB (μg/L)	2.0 (7.45)	1.95 (30.58)	$Z = -0.797$[a] $p = .426$
Troponin (ng/L)	1.0 (2.0)	3.3 (7.1)	$Z = -4.891$[a] **$p < .001$**
D-dimer mg/L	0.26 (0.5)	95.5 (207.5)	$Z = -5.783$[a] **$p < .001$**
First evaluation HADS-Anxiety scores ($n = 231$)	6 (6)	3.5 (6)	$Z = -1.671$[a] $p = .095$
First evaluation HADS-Depression scores ($n = 231$)	8 (8.75)	5 (5.25)	$Z = -3.309$[a] **$p = .001$**
Follow-up HADS-Anxiety scores ($n = 152$)	0 (3.75)	4 (6)	$Z = -5.713$[a] **$p < .001$**
Follow-up HADS-Depression scores ($n = 152$)	0 (3.75)	5 (6.25)	$Z = -6.371$[a] **$p < .001$**
SASSS ($n = 222$)	6 (7.5)	7 (8)	$Z = -0.641$[a] $p = .521$
First evaluation HADS-Anxiety frequency ($n = 231$)	19 (18.3)	25 (19.7)	$\chi^2 = 0.074$[b] $p = .785$
First evaluation HADS-Depression frequency ($n = 231$)	41 (39.4)	70 (55.1)	$\chi^2 = 5642$[b] **$p = .018$**
Follow-up HADS-Anxiety frequency ($n = 152$)	16 (18.2)	2 (3.1)	$\chi^2 = 8046$[b] **$p = .005$**
Follow-up HADS-Depression frequency ($n = 152$)	36 (40.9)	10 (15.6)	$\chi^2 = 11{,}224$[b] **$p = .001$**

Note: The significant values showed in bold type.

Abbreviations: CRP, C-reactive protein; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; Iqr, interquartile range, NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; SASSS, Severity of Acute Stress Symptoms Scale.

[a]Mann–Whitney *U* test. [b]χ^2 test. [c]Fisher's exact test.

COVID-19 clinical symptoms. Among the outpatient group, the female gender was more prevalent, years of education were longer, the employment rate was higher, and there were more patients with a history of psychiatric admission. Although the depression score was higher in patients who received outpatient treatment in the first evaluation, a decrease was observed after 1 month. The anxiety scores of inpatients and outpatients were not significantly different at the initial assessment whereas the inpatient group had higher anxiety scores after 1 month.

Sociodemographic and clinical characteristics and laboratory findings of inpatients and outpatients and their comparisons are presented in Table 2.

The correlation between laboratory findings and clinical characteristics (HADS-D and HADS-A scores for both evaluation and the SASSS) in inpatients and outpatients are presented in Table 3.

TABLE 3 Correlation between laboratory findings and clinical characteristics in outpatients and inpatients (Spearman's correlation analysis)

	First evaluation HADS-A	First evaluation HADS-D	1-month follow-up evaluation HADS-A	1-month follow-up evaluation HADS-D	SASSS
Age	−0.035	**0.148***	−0.117	−0.099	**−0.313****
CRP	0.025	**0.207***	−0.118	−0.042	−0.194
WBC	**−0.176***	−0.0104	−0.187	−0.079	−0.068
Neutrophil	**−.188***	−0.070	−0.125	−0.065	−0.140
Lymphocyte	−0.038	−0.099	−0.180	−0.144	0.108
NLR	−0.116	−0.015	0.005	0.047	**−0.179***
PLR	0.069	0.091	0.176	0.113	−0.121
Ferritin	**−0.326****	−0.145	**−0.298***	−0.203	**−0.389****
D-dimer	**0.214****	**0.286****	**−0.333****	**−0.294****	0.029
CK-MB	**−0.276***	−0.175	−0.196	**−0.367***	−0.172
Troponin	−0.043	−0.091	**−0.354****	**−0.349****	−0.084
SASSS	**0.634****	**0.456****	**0.423****	**0.307****	1.00

Note: The significant values showed in bold type.
Abbreviations: CRP, C-reactive protein; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; SASSS, Severity of Acute Stress Symptoms Scale; WBC, white blood cell.
*$p < .05$. **$p < .01$.

TABLE 4 Comparison between first evaluation and 4-week follow-up evaluation values (McNemar test) ($n = 153$)

	First evaluation *n* (%)	4-week follow-up evaluation *n* (%)	χ^2/ *p* ($n = 153$)
Sleep disturbance (yes)	84 (54.9)	27 (17.6)	$\chi^2 = 22.689$/ $p < .001$
Attention deficit (yes)	46 (30.1)	19 (12.4)	$\chi^2 = 30.248$/ $p < .001$
Irritability (yes)	44 (28.8)	25 (16.3)	$\chi^2 = 22.461$/ $p < .001$
Forgetfulness (yes)	41 (27)	32 (21)	$\chi^2 = 47.927$/ $p < .001$
Loss of taste (yes)	92 (60.1)	39 (25.5)	$\chi^2 = 26.351$/ $p < .001$
Loss of smell (yes)	100 (65.4)	48 (31.4)	$\chi^2 = 32.745$/ $p < .001$
Suicide plan (yes)	5 (3.3)	1 (0.7)	$\chi^2 = 29.795$/ $p < .001$
HADS-A (above cutoff score)	31 (20.5)	18 (11.8)	$\chi^2 = 33.160$/ $p = .011$
HADS-D (above cutoff score)	69 (45.7)	46 (30.3)	$\chi^2 = 24.178$/ $p < .001$

Abbreviations: HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale.

Comparison of initial and final evaluation scores

Comparisons between the initial and follow-up clinical evaluations of the 153 patients who were reevaluated 1 month after the initial evaluation are presented in Table 4. The percentage of sleep problems, $p < .001$, attention problems, $p < .001$, forgetfulness, $p < .001$, irritability, $p = .002$, loss of taste, $p < .001$, loss of smell, $p < .001$, and making suicide plans, $p < .001$, in patients significantly decreased between the initial evaluation and 1 month later. In addition, the frequency of anxiety (scored above the cutoff point in the HADS-A) and depression (scored above the cutoff point in the HADS-D) decreased between the initial and the follow-up evaluation, ($p = .011$ and .001, respectively).

Two-way rmANOVA results

A comparison of the initial and follow-up depression scores of the patients according to sociodemographic and clinical characteristics was evaluated using two-way rmANOVA. Accordingly, there was a statistically significant decrease between the depression scores measured at baseline and follow-up. According to rmANOVA, there was no main effect of time, $F(1,30) = 0.002$, $p = .964$, gender, $F(1,30) = 1.99$, $p = .168$, treatment modality, $F(1,30) = 2.05$, $p = .163$, presence of pneumonia, $F(1,30) = 2.57$, $p = .119$, psychiatric disease history, $F(1,30) = 0.004$, $p = .948$, loss of smell, $F(1,30) = 2.31$, $p = .117$, loss of taste, $F(1,30) = 2.49$, $p = .1$, age, $F(1,30) = 4.06$, $p = .923$, or education status, $F(1,30) = 2.04$, $p = .053$, on the change in depression score. There was a significant interaction between time and treatment modality, $F(1,30) = 15.11$, $p = .001$; accordingly, depression scores of the inpatient group definitely decreased over time, and outpatients displayed slightly increased depression scores in this period, $p < .001$ (Figure 2).

Comparisons of anxiety scores at baseline and at 1-month follow-up according to sociodemographic and clinical features were assessed with two-way rmANOVA. Treatment modality, $F(1,30) = .37$, $p = .550$, presence of pneumonia, $F(1,30) = .43$, $p = .516$, psychiatric disease history, $F(1,30) = .03$, $p = .869$, loss of smell, $F(1,30) = .78$, $p = .467$, loss of taste,

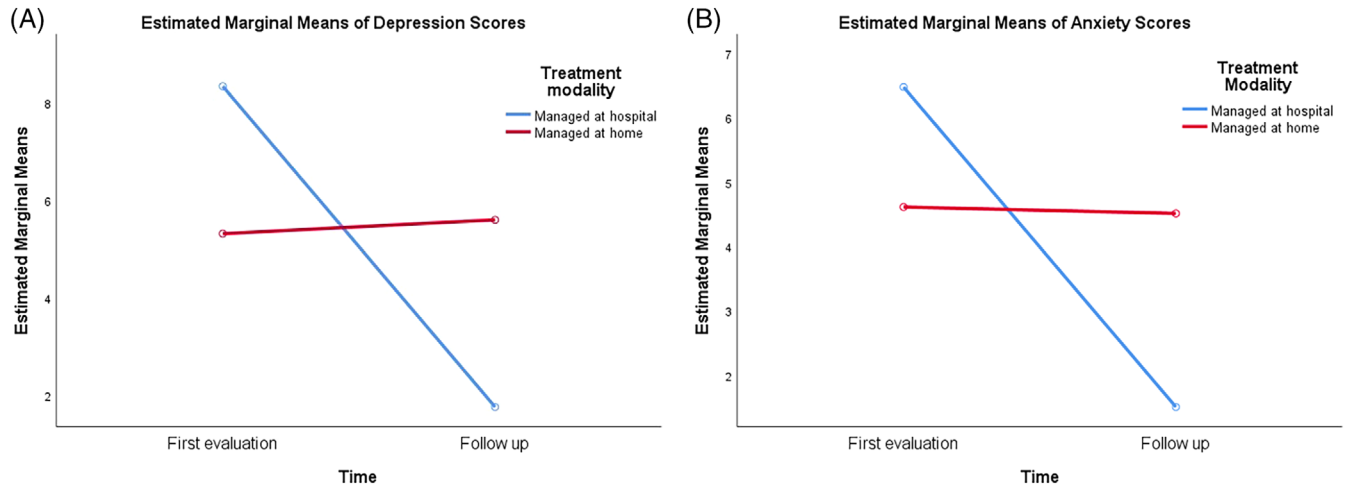

FIGURE 2 (A) Change in HADS-Depression subscale scores over time in outpatients and inpatients. (B) Change in HADS-Anxiety subscale scores over time in outpatients and inpatients

$F(1,30) = .86$, $p = .435$, age, $F(1,30) = .167$, $p = .685$, and education status, $F(1,30) = .21$, $p = .648$, had no main effect on anxiety scores; on the contrary, gender had a main effect on anxiety scores, $F(1,30) = 4.56$, $p = .041$. In addition, there was a significant interaction between treatment modality (inpatient/outpatient) and the change in anxiety scores, $F(1,30) = 10.18$, $p = .003$. Anxiety scores decreased over time in the inpatient group whereas anxiety scores are nearly the same in the outpatient group, $p = .003$ (see Figure 2B).

The Change in HADS-A and HADS-D scores over time in outpatients and inpatients are presented in Figure 2B.

DISCUSSION

In this follow-up study, the severity of depression, anxiety, and acute stress and the factors predicting these symptoms were examined 3–7 days and 1 month after diagnosis of COVID-19 by polymerase chain reaction (i.e., PCR) test. Anxiety and depression scores are reported as the most common psychiatric presentations in the acute and post-illness phases of COVID-19 infection (Deng et al., 2020; Rogers et al., 2020). During the first phase of our study, depression and anxiety scores were above cutoff levels in 55.1% and 19.7% of hospitalized inpatients, respectively, and in 39.4% and 18.3% of outpatients, respectively. A meta-analysis that included 25 studies addressing anxiety symptoms reported that the prevalence of anxiety was 47% among patients hospitalized due to COVID-19 infection (Deng et al., 2020). This high rate may be attributed to the inclusion of patients with various clinical progressions in the meta-analysis. Zhang et al. (2020) evaluated patients with mild and moderate disease severity, as in our study sample, and reported the prevalence of anxiety was 20%, which is consistent with the results of our study. In the meta-analysis by Deng et al. (2020), 23 studies were evaluated to determine the prevalence of depression, revealing a rate of 45%, which is consistent with our study's findings.

In studies conducted during the post-COVID-19 period, the prevalence of depression was between 10% and 31%, and the prevalence of anxiety was between 18% and 42% (Liu et al., 2020; Mazza et al., 2020; Poyraz et al., 2021). In our study, we found that depression was above the cutoff score in 30.3% of the patients, and anxiety was above the cutoff score in 11.8% of patients 4 weeks after the first diagnosis. Differences between the results of the studies may be related to the severity of the illness or the number of weeks after acute infection. Our study only included patients with mild and moderate severity, and none of the patients required intensive care in a later period; therefore, anxiety and depression levels of the patients may have remained low during the follow-up period. The inclusion of outpatients and inpatients allowed us to examine the effects of different treatment modalities on anxiety and depression symptoms and the course of these symptoms. The main factor affecting anxiety and depression was treatment modality. Although there was no significant difference between inpatients and outpatients during the acute period in terms of anxiety scores, hospitalized inpatients had higher depression scores compared to outpatients. In the evaluation, 1 month after the diagnosis, a more significant decrease in the frequency of both anxiety and depression was observed in inpatients compared to outpatients. Considering that all patients who were hospitalized were discharged at the end of the first month, this difference may be due to the elimination of the stress caused by hospitalization. In a qualitative study, Hao et al. (2020) reported that patients who were hospitalized due to COVID-19 experienced loneliness, discomfort due to physical conditions, and hopelessness, and that these experiences may be related to symptoms of anxiety and depression. Kong et al. (2020) stated that feeling a lack of social support may increase symptoms of anxiety and depression. A change in these conditions after discharge may have provided a significant improvement in symptoms compared to outpatients. This may indicate the need for psychological support during inpatient treatment. The depression scores were higher at follow-up

compared to the acute period in outpatients. Although it has been noted in the literature that inpatients may feel uncomfortable due to hospital conditions, being protected within the health system and being under the supervision of a doctor or nurse may reinforce the feeling of well-being while recovering in the clinic. In support of this, anxiety is high during hospitalization, but this may indicate the anxiety of hospitalization. Outpatients may need a support system where they can feel protected within the healthcare system. We also should keep in mind that during the follow-up period, outpatients may need evaluation for psychiatric symptoms.

It is thought that the immunological effects of COVID-19 play a significant role in the emergence of psychiatric symptoms; in particular, cytokine storm is thought to further trigger psychiatric symptoms (Dantzer, 2018; Netland et al., 2008). In our study, a weak positive correlation between CRP level and HADS-D scores was observed. Previous studies have reported a weak correlation between elevated CRP and major depression and psychological stress (Köhler-Forsberg et al., 2017; Strawbridge et al., 2015; Wium-Andersen et al., 2013). In our study, a weak to moderate positive correlation was observed between D-dimer levels and the HADS-A and HADS-D scores measured at the 1-month follow-up. Von Känel et al. (2009) reported that D-dimer level may be associated with long-term burnout syndrome and depressive symptoms. The fact that D-dimer is one of the prognostic markers for COVID-19 disease makes it difficult to interpret the relationship found between the symptoms of anxiety and depression and D-dimer levels. Nevertheless, it supports the notion that the immune response induced by the infection plays a role in the emergence of psychiatric symptoms. In our study, a moderate inverse relationship was found between troponin level and HADS-A and HADS-D measurements during follow-up. Benitez et al. (2009) found a moderate inverse correlation between troponin levels and depressive symptoms in their study of elderly individuals, and stated that this may be because the troponin levels found in their study were much lower than the levels in studies reporting a positive relationship between elevated troponin and depression. In our study, troponin levels were also much lower than those reported in other studies, and the fact that troponin levels were measured in a very small number of patients may have contributed to this finding. Debnath et al. (2020) conducted a review on the inflammatory processes of the COVID-19 infection and emphasized that the subchronic inflammatory response and cytokine storm may play a role in the emergence of neuropsychiatric symptoms. Because our patients had mild and moderate illnesses and none of them developed cytokine storms may indicate that the inflammatory system was not strongly stimulated in the acute period; therefore, we could not establish a clear link between them. In our study, the main factor affecting anxiety and depression was inpatient treatment, and the fact that biomarkers related to inflammation were not studied in the majority of outpatients may have limited the evaluation of biomarkers. Long-term neuropsychiatric effects of inflammation should be observed in these patients.

Loss of smell is observed in 80%–90% of Covid-19 patients (Lechien et al., 2020; Sedaghat et al., 2020; Yan et al., 2020), often together with loss of taste. In patients with loss of smell and taste, COVID-19 infection often progresses with more severe symptoms, such as shortness of breath (Speth et al., 2020). Studies unrelated to COVID-19 have reported that loss of smell and taste increases the risk of anxiety and depression (Erskine & Philpott, 2020; Hur et al., 2018). Therefore, the prevalence of psychiatric symptoms in COVID-19 patients with loss of smell and/or taste is an interesting question. Speth et al. (2020) reported that loss of smell and taste was associated with anxiety and depression in their 6-week follow-up study, and they claimed that the relationship between chemoreceptor disorder and mood disorder may be due to the neurotropic effects of the virus. In our study, the prevalence of loss of smell and taste was 65% and 60%, respectively, and these patients scored higher on the anxiety and depression scales both in the first phase and at the 1-month follow-up. Furthermore, at 1-month follow-up, forgetfulness was found in 29% and attention deficit in 18% of patients with loss of smell. These cognitive symptoms may be related to the anxiety and depression symptoms of the patients as well as due to the neuroinflammatory effects of COVID-19. To differentiate the two, it is necessary to investigate the psychiatric, neurological, and immunological parameters in more detail in larger samples.

LIMITATIONS

Our study had some limitations. To form a homogeneous study sample and collect data directly from patients, only mild-to-moderate COVID-19 patients were included in our study. This circumstance may have been the reason for the low inflammatory response; therefore, the possible effect of parameters related to inflammatory processes on psychiatric symptoms could not be properly evaluated. The relationship between cytokine storm and psychiatric complications should be examined in a study on patients with severe illness. Another limitation of the study was that the psychiatric symptoms of the patients could not be evaluated by a psychiatrist due to home-isolation requirements, and self-reporting scales were used instead. A follow-up evaluation was conducted 4 weeks after the initial evaluation; however, only 65% of patients could be contacted, which was another limitation of the study.

CONCLUSION

The incidence of psychiatric symptoms, such as anxiety and depression, is quite high in the acute period of patients with mild/moderately severe COVID-19 infection. These symptoms significantly improve within 4 weeks. Symptoms of anxiety and depression were more severe in inpatients, but these patients showed a greater improvement in symptoms at follow-up. Although it is said in the literature that inpatients may feel uncomfortable due to hospital conditions, being protected within the health system and being under the supervision of a doctor or nurse may reinforce the feeling of well-being while recovering in the clinic. Loss of smell and taste in

the patient may be a significant indicator that the symptoms of anxiety and depression will persist during the follow-up period. A weak relationship was found between psychiatric symptoms and CRP, troponin, and D-dimer in patients with mild/moderate COVID-19 infection, but this should be investigated in larger studies.

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CONFLICT OF INTEREST

There is no conflict of interest.

ETHICS STATEMENT

The study received approval from the Başkent University Ethics Committee (ref. KA20/178) and written and oral consent was obtained from all participants.

DECLARATION OF COMPETING INTERESTS

The authors declare no competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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