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RESEARCH

Six-month psychiatric outcomes among survivors of COVID-19

COVID-19 enfeksiyonu geçiren bireylerde altı ay içinde görülen ruhsal bozukluklar

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Abstract

Purpose: Long-lasting COVID-19 symptoms are closely associated with psychiatric sequelae. However, little is known about whether it is possible to predict a protracted course early in the disease. In this study, we aimed to understand how post-COVID-19 psychiatric symptomatology evolves over time and the variables that affect these symptoms.

Materials and Methods: Anxiety, depression, acute stress, and sleep disorders among patients with COVID-19 were prospectively evaluated during hospitalization and six months after discharge. Adult patients recently admitted to non-intensive care units with COVID-19 were eligible. Their psychiatric status was assessed using the Hospital Anxiety and Depression Scale, National Stressful Events Survey Acute Stress Disorder Short Scale, Pittsburgh Sleep Quality Index. The patients' clinical data were gathered from hospital records. Six months after they were discharged, the same questionnaire and a checklist to assess ongoing physical symptoms were distributed to the patients via WhatsApp.

Results: 143 participants were enrolled, 47 of whom completed the study. The results showed that patients' depression, anxiety, and insomnia significantly decreased during the follow-up. However, there was an increase in the number of patients who reported acute stress symptoms. The highest C-reactive protein level during acute infection (OR=1.09) predicted depression during the follow-up. Experiencing a higher number of infectious symptoms during hospitalization predicted a higher number of protracted symptoms six months later (OR=1.5).

Conclusion: This indicates that the severity of systemic inflammation during acute COVID-19 infection may predispose patients to persistent depression. Patients with

Öz

Amaç: Bir hastanın Covid-19 semptomları gösterdiği sürenin uzaması ruhsal bozukluklarla yakından ilişkilidir. Bununla birlikte, hastalığın erken evrelerinde kimde belirtilerin uzun süreceğini öngörmenin mümkün olup olmadığı hakkında çok az şey biliniyor. Bu çalışmada Covid-19 sonrası psikiyatrik semptomların zamanla nasıl geliştiğini, bu semptomları etkileyen değişkenleri anlamayı amaçladık.

Gereç ve Yöntem: Covid-19 hastaları hastanede yatarken ve taburcu olduktan sonraki altı ay içinde gösterdikleri kaygı, depresyon, akut stres ve uyku bozuklukları açısından uzun dönemli olarak değerlendirildi. Yakın zamanda Covid-19 ile yoğun bakım dışındaki birimlere kabul edilen yetişkin hastalar çalışma kapsamına alındı. Ruhsal durumları, Hastane Kaygı ve Depresyon Ölçeği, Ulusal Ölçekte Stresli Olaylar Anketi, Akut Stres Bozukluğu Ölçeği Kısa Formu, Pittsburgh Uyku Kalitesi Endeksi kullanılarak değerlendirildi. Hastaların klinik verileri hastane kayıtlarından derlendi. Taburcu olduktan altı ay sonra hastalara aynı soru formu ve dirençli fiziksel semptomların değerlendirilmesi için de bir semptomlar listesi WhatsApp aracılığıyla gönderildi.

Bulgular: Çalışmaya dahil edilen 143 katılımcıdan 47'si çalışmayı tamamladı. Sonuçlar hastaların depresyon, anksiyete ve uykusuzluğunun takip sırasında önemli ölçüde azaldığını gösterdi. Ancak akut stres semptomları bildiren hasta sayısında artış oldu. Akut enfeksiyon sırasındaki en yüksek C-reaktif protein seviyesi (OR=1.09), takip sırasındaki depresyonu öngörmüştür. Hastanede yatış sırasında daha fazla enfeksiyöz semptom yaşamanın, altı ay sonra daha fazla sayıda uzamış semptom öngördüğü saptandı (OR=1.5).

Sonuç: Akut Covid-19 enfeksiyonu sırasındaki sistemik iltihaplanmanın şiddeti depresyon belirtilerinin

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a higher number of symptoms during acute infection may be at risk of developing long-term COVID-19.

Keywords:. Anxiety, depression, post-traumatic stress, protracted symptoms, COVID-19, inflammation.

direnmesine yol açabilir. Buna göre, akut enfeksiyon sırasında daha çok sayıda semptom gösteren hastalar uzamış Covid-19 hastalığı geçirme tehlikesi altında olabilirler.

Anahtar kelimeler: Anksiyete, depresyon, travma sonrası stres, uzun süreli semptomlar, COVID-19, inflamasyon.

INTRODUCTION

Despite the development of effective vaccines against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus has continued to mutate. As of December 2021, Coronavirus Disease 2019 (COVID-19) cases are significantly rising worldwide owing to the new and highly transmissible Omicron variant, which reportedly causes a milder illness. The pandemic has resulted in the death of over 5.5 million people and has devastated the mental health of individuals globally. However, the long-term mental health outcomes of people who have recovered from COVID-19 are yet to be examined.

Previous cross-sectional studies revealed that patients who recovered from COVID-19 showed clinically significant symptoms of anxiety, depression, fatigue, and insomnia in the month following their discharge[1-5]. Most longitudinal studies reported that anxiety and depressive symptoms improved with time once the acute illness subsided[4,6,7]. However, some patients displayed psychiatric symptoms that persisted for several months and caused functional disabilities. The underlying mechanisms of persistent depressive/anxiety symptoms and protracted physical symptoms defined as "long COVID" in the literature have not been elucidated. Additionally, both of these appear to be multifactorial phenomena. It has been previously suggested that the host's immune response to SARS-CoV-2 infection and psychological stress before and during infection[8,9] may contribute to neuropsychiatric sequelae[10].

Chronic low-grade inflammatory responses have been implicated in the development of the neuropsychiatric manifestations of SARS-CoV-2 infection[11]. Activated neuroinflammatory pathways may cause psychiatric symptoms. Influenza, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) have been shown to induce a hyperinflammatory state and are associated with neuropsychiatric symptoms. Chronic low-grade inflammation or other immunological alterations observed during SARS-CoV-2 infection may potentially impact the development of medium- and long-term psychiatric symptoms once the infection subsides. Thus far, few studies have examined the impact of systemic inflammation severity during acute infection on psychiatric sequelae. Mazza et al. found that systemic inflammation at admission predicted the severity of depressive psychopathology during post-discharge follow-ups (at one month and three months). Furthermore, higher depression in convalescent patients with COVID-19 was consistently associated with a higher neutrophil/lymphocyte ratio and higher CRP levels[12].

In this study, we aimed to understand how post-COVID-19 psychiatric symptomatology evolves over time. We hypothesized that COVID-19 survivors (treated in the hospital setting) would demonstrate the subsidence (but not disappearance) of psychiatric symptoms. We aimed to examine whether the severity of the initial systemic inflammation affects long-term anxiety and depression. Additionally, we aimed to measure the prevalence of persistent physical symptoms (fatigue, dyspnea, and pain) six months after the patients' discharge, and explore the associated risk factors.

MATERIALS AND METHODS

Design and study population

We investigated the longitudinal psychological effects of COVID-19 infection on patients hospitalized with a confirmed COVID-19 diagnosis[13] by conducting a follow-up study six months after their discharge. Prior to commencing the study, ethical clearance was sought from the İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee with 83045809-604.01.02-62424 protocol number at 15.05.2020. The initial assessments were conducted between June 2020 and February 2021 at the İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine tertiary hospital in Istanbul, Turkey. Screening for inclusion in the study was performed as soon as an enrolled patient was admitted from the emergency department to an inpatient (non-ICU) hospital service. Patients were informed about research and taken their informed consent orally and in written.

We included patients aged 18 years or older, who had tested positive for COVID-19 and were currently hospitalized for treatment and had the capacity to provide informed consent. The patients who had active psychiatric pathology, had any cognitive disability, or had a history of substance abuse or dependence, were excluded. Having a history of psychiatric diagnosis was not exclusion criterion. Eligible patients were contacted by two trained psychiatrists on approximately the seventh day of hospitalization, who conducted a brief unstructured clinical interview to check for any major psychopathology. A total of 143 patients were interviewed.

In the second step of the study, the investigators contacted the participants for a follow-up assessment six months after their discharge. For this, an online survey hosted on Google Forms was sent to the participants via WhatsApp. To ascertain the long-term medical effects of COVID-19, the participants were also sent a symptom checklist to report any ongoing COVID-19 symptoms. The online survey received 47 responses (response rate: 32%). Four patients had died from any medical causes after their discharge. The flowchart was shown the stages of the present study (Figure 1).

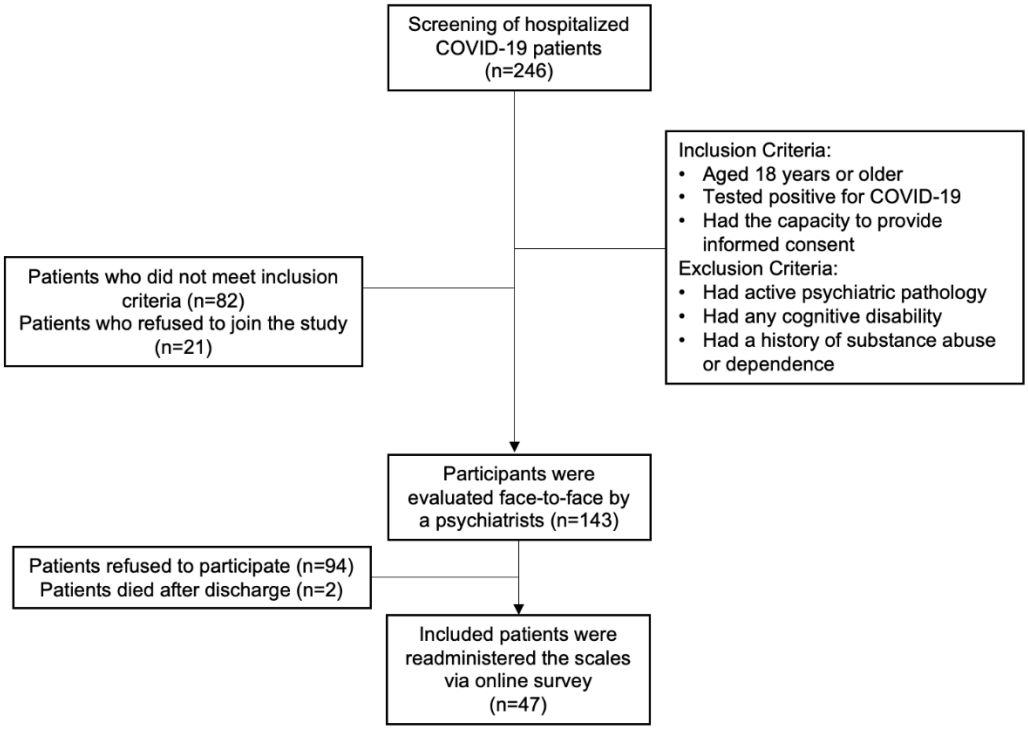

Figure 1. Flowchart of sample

Clinical and psychological assessment

A self-report questionnaire was administered to collect sociodemographic variables of interest (age, gender, educational, marital and employment status, monthly family income), medical status (history of chronic diseases and psychiatric disorders), and additional information relevant to the outbreak and lockdown conditions (history of

COVID-19 among the patient's family and relatives/friends, financial hardship [not enough money for basic needs] due to the pandemic). The participants' medical files were reviewed for information regarding the clinical severity of their infection, length of hospitalization, and lowest oxygen saturation levels on pulse oximetry. The severity of infection is defined according to WHO guidelines. Stage 1 (mild disease) corresponds to patients with symptomatic infection but no evidence of hypoxia or pneumonia. Stage 2 (moderate disease) is described as mild pneumonia with SpO2 ≥ 90% on room air. Stage 3 (severe disease) corresponds to severe pneumonia with SpO2 < 90% on room air. Stage 4 (critical disease) includes Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, and acute thrombosis. Patients' inflammatory markers at hospital admission during acute COVID-19 infection were ascertained based on the treatment agents administered to them and their highest C-reactive protein (CRP) and D-dimer levels as per their charts.

Measures

The Hospital Anxiety and Depression Scale (HADS) was used to assess patients' symptoms of depression and anxiety [14]; the National Stressful Events Survey Acute Stress Disorder Short Scale (NSESSS) [15] was used to ascertain their stress levels, and the Pittsburgh Sleep Quality Index (PSQI) was used to identify whether they experienced sleep disturbances[16].

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-report questionnaire developed to evaluate anxiety and depression symptoms in patients with physical illnesses. The scale consists of 14 items, each rated on a four-point scale ranging from 0 to 3. Seven items for each anxiety and depression subscales calculate separately. Higher scores indicating greater severity of symptoms. The Turkish version of HADS has been translated and validated for use in the Turkish population. The Cronbach's alpha coefficient was 0.85 for the anxiety subscale and 0.78 for the depression subscale. The HADS cut-off scores established as appropriate for Turkish populations were used to consider the presence of psychopathology (7 for anxiety and 10 for depression)[17].

National Stressful Events Survey Acute Stress Disorder Short Scale (NSESSS)

The National Stressful Events Survey Acute Stress Disorder Short Scale (NSESSS) is a self-report measure designed to assess acute stress disorder symptoms following a traumatic event. The Turkish version of NSESSS has been translated and validated for use in the Turkish population. As for the NSESSS, a score of 0 suggested no acute stress disorder, whereas scores of 1, 2, 3, and 4 points corresponded to mild, moderate, severe, and extreme symptoms, respectively. The items cover symptoms which are flashbacks, intrusion, avoidance, arousal, dissociation, and pervasive negative mood. The scores for the items are summed to yield a total score, with higher scores indicating greater severity of acute stress disorder symptoms. The scale can help clinicians identify individuals who may need further assessment or treatment for acute stress disorder. For NSESSS, Ascibasi et al. found adequate internal consistency in the Turkish population, with a Cronbach's alpha score of 0.95[18].

We used NSESSS to evaluate patients' stress levels at both time points, rather than using National Stressful Events Survey PTSD Short Scale (NSESSS-PTSD) at the sixth-month follow-up. In terms of psychometric properties, both scales have demonstrated good reliability and validity. NSESSS-PTSD has 9 questions to assess PTSD symptoms, five of which are the same as the NSESSS. Our aim for using this instrument was to evaluate patients' trauma-related symptoms, not diagnose PTSD. Although, NSESSS-PTSD is more sensitive to detect PTSD than NSESSS, comparing the same scale scores at different time points provides a more accurate statistical analysis.

Pittsburgh Sleep Quality Index (PSQI)

It is a self-report scale that assesses sleep quality over the last month. The Turkish version of the PSQI has been well validated for use in the Turkish population. The scale consists of 19 items that cover seven components of sleep quality, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The subscores are summed to yield a global score, ranging from 0 to 21, with higher scores indicating poorer sleep quality. The Turkish version of the PSQI has been found to have good reliability and validity in several studies, with Cronbach alpha score was 0.75. A generalized

accepted cut-off score of 5 was used with regard to the PQSI.

During their hospitalization, participants were asked to report their personal views of the general severity of their symptoms. The scores for the same could range from 0 (no symptoms) to 5 (very severe symptoms). In addition, a checklist that queried whether the participants experienced an alteration in their sense of smell/taste, headache, fatigue, daytime sleepiness, muscle aches, lightheadedness, difficulty in concentration, and numbness and tingling sensations was provided to them both during hospitalization and at follow-up[19].

Statistical analysis

We reported the characteristics of the enrolled patients as numbers and percentages. Descriptive statistical analyses were performed for categorical and continuous variables of interest. Results were expressed as mean ± standard deviation or number (%). The Kolmogorov–Smirnov test was used to assess the normal distribution of the quantitative data. Paired or independent sample t-tests were used when necessary, and non-parametric tests were used to compare non-normally distributed data to evaluate mean differences. The chi-square test was used to compare categorical variables. Pearson's correlation was used to calculate associations, and the nonparametric equivalent of the unpaired t-test was used to compare means between two groups.

To investigate the effects of gender and psychiatric history on changes in psychopathology over time, repeated measures ANOVAs were performed with consideration of the patients' HADS-A, HADS-D, and NSASSS scores during hospitalization and six months after discharge.

We also performed a binary logistic regression analysis to predict the severity of protracted symptoms using the median of protracted symptoms as the cut-off point for the outcome variable (0−2 symptoms versus >3 symptoms), and the presence of considerable depression and anxiety symptoms using the cut-off point of HADS at six months; we selected the significant variables as independent predictors. All tests were two-tailed with a significance level of $p<0.05$. Statistical analyses were performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA).

RESULTS

A total of 143 hospitalized patients with a confirmed COVID-19 diagnosis were enrolled in the study (WHO criteria, 2020). A total of 47 (32%) patients completed the initial and follow-up assessments. The follow-up was performed between June 2021 and September 2021.

Those who only participated in the initial assessment were significantly older than those who participated in both assessments ($p=0.03$, $t=-3.05$, $df=119$). There were no gender differences between those who only participated in the initial assessment and those who participated in both assessments ($p=0.6$, $df=1$, $X2=0.282$). In addition, patients diagnosed with stage 1 (n=4) and stage 4 (n=8) COVID-19 were among those who only participated in the initial assessment, whereas those who participated in both assessments were diagnosed either with stage 2 (n=22) or stage 3 (n=25) COVID-19 ($p=0.002$, $df=4$, $X2=16.9$).

The participants' (N=47) mean age was 43.7 years (SD=13.9). They consisted of 25 men (52.8%) and 22 women (46.8%). A majority of them were married (66%), half of them were employed, and 30% of them had at least completed university education.

A total of 42% of the participants reported that they underwent financial hardship due to the pandemic. Additionally, 59.4% had family members or relatives with a history of COVID-19 infection. Thirteen (27.7%) participants had a past psychiatric history (anxiety or depressive disorder). The participants were categorized into two groups based on the severity of their COVID-19 infection during their hospitalization; 22 (46.8%) of them were diagnosed with stage 2 COVID-19 (symptomatic without pneumonia), whereas 25 (53.2%) were diagnosed with stage 3 COVID-19 (pneumonia not requiring oxygen) (Table 1).

Comorbidities reported by the patients included diabetes mellitus (n=7; 14.9%), congestive heart failure (n=4; 8.5%), hypertension (n=2; 4.3%), and other chronic diseases (n=24; 51%). The most common medication used during their hospitalization was favipiravir (n = 35; 73.9%), followed by hydroxychloroquine (n=26; 56.5%), antibiotic (n=30; 63.8%), corticosteroids (n=11; 23.4%), and remdesivir (n=1; 2.1%). The demographic and clinical data of our cohort are provided in Table 1.

Table 1. Cohort demographic data (n=47)

Variables		Mean±SD / n(%)
Age		43.7±14
Gender		
	Female	22 (46.8%)
	Male	25 (53.2%)
Education		8.4±4.8
Marital status		
	Single	16 (34%)
	Married	31 (66%)
Employment status		
	Employed	24 (51.1%)
	Unemployed	23 (48.9%)
Financial hardship due to pandemic		
	Yes	20 (42%)
	No	27 (58%)
COVID-19 stage		
	2	22 (46.8%)
	3	25 (53.2%)
Treatment		
	Cortisol	11 (23.4%)
	Hydroxychloroquine	26 (55.3%)
	Favipiravir	35 (74.4%)
	Antibiotic	30 (63.8%)
	Remdesevir	1 (2.1%)
	Oseltamivir	6 (12.8%)
	Tocilizumab	3 (6.4%)
	Plasmapheresis	1 (2.1%)
Additional diagnosis		
	HT	5 (7.2%)
	DM	11 (15.9 %)
	COPD	1 (1.4%)
	Asthma	6 (8.7%)
	CAD	31 (44.9%)
	Others	15 (21.7%)
	None	5 (7.2%)
Family/relatives with COVID-19		
	Yes	28 (59.4%)
	No	19 (40.6%)
Past psychiatric history (anxiety/depressive disorders)		
	Yes	13 (27.7%)
	No	34 (72.3%)

HT=hypertension; DM= diabetes mellitus; COPD=chronic obstructive pulmonary disease, CAD=coronary artery disease

The mean length of their hospital stay was 6.1 days (SD=3.7), and their mean lowest oxygen saturation during their hospital stay was 92.1 (SD=4.6). As for inflammatory markers, their mean highest C-reactive protein level during hospitalization was 38.6 (mg/L) (SD=42.2), and their mean highest D-dimer level during hospitalization was 18.5 (SD=24.4) (Table 2).

Table 2. Cohort clinical data (n=47)

Inflammatory markers	Mean±SD
Highest C-reactive protein (ref 0-5 mg/L) during admission (mg/L)	38.6±42.4
D-Dimer (ref 0-0.5 mg/L) highest during admission	18.5±24.4
Length of hospital admission (d)	6.2±3.7
Lowest O2 saturation	92.1±4.5

During hospitalization, 42.6% of the patients reported considerable anxiety symptoms (HADS-A score >10), and their mean anxiety score was 6.4 ± 3.8. Far fewer patients (10.6%) reported considerable anxiety symptoms when assessed six months after discharge, and their mean anxiety score was 4.9 ± 3.7 (p=0.04, t=2.1, df=46). The effects of gender and psychiatric history on the changes in level of anxiety symptoms were investigated. The generalized linear model analysis revealed no significant effect with respect to gender (Mauchley's W(P)=0.231; Wilks'λ=0.90; F=1.17; p>0.05) or past psychiatric history (Mauchley's W(P)=0.08; Wilks'λ=0.90; F=3.08; p>0.05).

During hospitalization, 19.1% of the patients reported considerable symptoms of depression (HADS-D score >10), and their mean depression score was 7.2 ± 3.8. Far fewer (12.8%) of them reported considerable symptoms of depression when assessed six months after discharge, and their mean depression score was 5.5 ± 3.8 (p=0.02, t=2.5 df=46). The effects of gender and psychiatric history on the changes in level of depression were investigated. The generalized linear model analysis revealed no significant effect with respect to gender (Mauchley's W(P)=0.971; Wilks'λ=0.991; F=0.001; p>0.05) or past psychiatric history ((Mauchley's W(P)=0.993; Wilks'λ=0.995; F=0.336; p>0.05).

The participants' mean NSASSS score during hospitalization was 1 (SD = 0.6), but increased to 1.4 (SD = 0.8) during the follow-up. This increase was statistically significant (p=0.03, t=-2.3, df=46). During hospitalization, 59.6% of the participants displayed mild symptoms of acute stress disorder, whereas 17% and 2.1% of them displayed moderate and severe symptoms, respectively. However, during the follow-up, 38.3% of the participants reported experiencing mild symptoms, whereas 36.2% and 8.5% of them experienced moderate and severe symptoms of acute stress disorder, respectively. The effects of gender and past psychiatric history on the changes in acute stress symptoms were investigated. The generalized linear model analysis revealed no significant effect with respect to gender (Mauchley's W(P)=0.388; Wilks'λ=0.983; F=0.76; p>0.05) or past psychiatric history (Mauchley's W(P)=0.632; Wilks'λ=0.995; F=0.233; p>0.05).

Patients whose family members/relatives also had COVID-19 displayed an increased severity in acute stress symptoms during the follow-up compared with those whose family members/relatives did not have COVID-19 (p=0.003, t=3.2, df=45). Additionally, women displayed an increased severity in acute stress symptoms during the follow-up compared to men (p=0.06, t=1.8, df=45).

The participants' mean PSQI total score during hospitalization was 5.5 (SD=2.8). During the follow-up, it decreased to 4.1 (SD=2.5; p=0.006, Wilcoxon=-2.7). A total of 24 (51.1%) patients experienced probable sleep disturbance (>5 points) during hospitalization, whereas 11 (23.4%) of them experienced probable sleep disturbance when assessed six months later (p=0.09, X_2=2.7, df=1). Also, statistically significant mean changes in subscale scores were detected over time. The scores of subscales decreased during the follow-up: subjective sleep quality 1.4 (SD=0.6) to 1.1 (SD=0.5) (p=0.005, Wilcoxon=-2.8), sleep duration 0.4 (SD=0.6) to 0.2 (SD=0.4) (p=0.02, Wilcoxon=-2.3), sleep disturbances 1.9 (SD=0.6) to 1.6 (SD=0.5) (p=0.01, Wilcoxon=-2.6), daytime dysfunction 0.7 (SD=0.5) to 0.3 (SD=0.5) (p=0.002, Wilcoxon=-3.16). None of the patients were taking sleep medication.

Patients with a psychiatric history had significantly higher HADS-A scores (p=0.004, t=3.04, df=45) and acute stress symptoms scores (p=0.017, t=2.5, df=45) during hospitalization than those without one. However, the HADS-D scores of the two groups did not differ significantly (p=0.6, t=45, df=-0.4). The HADS-A (p=0.58, df=45, t=0.55), HADS-D (p=0.76, df=45, t=0.3), and NSASSS (p=0.91, t=-0.11, df=45) scores of the two groups did not differ when assessed six months later. All results of the scales comparisons were depicted in Table 3.

Table 3. Comparison between initial and follow-up assessments

		Initially	**Six months later**			
Screening Test		Mean (SD)	Mean (SD)	p	t/X2	df
HADS-A		6.4 (3.8)	4.9 (3.7)	0.04	2.1	46
HADS-D		7.2(3.8)	5.5 (3.8)	0.02	2.5	46
NSESSS		1 (0.7)	1.4 (0.9)	0.03	-2.3	46
PSQI						
	Total Score	5.5 (2.8)	4.1 (2.5)	0.006	-2.7	
	Subjective sleep quality	1.4 (0.6)	1.1 (0.5)	0.005	-2.8	
	Sleep latency	1.1 (0.7)	0.9 (0.7)	0.16	-1.4	
	Sleep duration	0.4 (0.6)	0.2 (0.4)	0.02	-2.3	
	Habitual sleep efficiency	0.1 (0.6)	0.06 (0.4)	0.56	-0.6	
	Sleep disturbances	1.9 (0.6)	1.6 (0.5)	0.01	-2.6	
	Daytime dysfunction	0.7 (0.5)	0.3 (0.5)	0.002	-3.16	

HADS = Hospital Anxiety and Depression Scale; NSESSS = National Stressful Events Survey Acute Stress Disorder Short Scale; PSQI= Pittsburgh Sleep Quality Index

Persistent physical symptoms

During their hospitalization, 20 (42.6%) participants reported experiencing mild physical symptoms, whereas 27 (57.4%) of them reportedly experienced moderate physical symptoms. The most frequently reported physical symptoms during hospitalization were fatigue (100%), cough (48%), dyspnea (60%), myalgia (71%), loss of taste/smell (29%), headache (27%), and abdominal pain (12.5%). The mean number of symptoms experienced by the patients was 6.04±5.07.

During the follow-up, 31 (66%) patients reported experiencing mild physical symptoms, whereas 16 (34%) of them reportedly experienced moderate physical symptoms. During the follow-up, a total of 27 participants reported experiencing between zero to two protracted symptoms, whereas 20 of them experienced three or more symptoms. The most frequently reported persistent symptoms during the follow-up were fatigue (76%), abdominal pain (68%), headache (33%), alteration of taste/smell (12.5%), difficulty in concentration (21%), and light headedness (12.5%).

Correlation analysis

The participants' highest C-reactive protein levels during hospitalization were positively correlated with their HADS-A (r=0.695, p<0.001) and HADS-D (r=0.731, p<0.001) scores during the follow-up. Their highest D-dimer levels during hospitalization were positively correlated with their HADS-D scores during the follow-up (r=0.3, p=0.039).

The participants' total number of protracted symptoms was positively correlated with their HADS-D scores during the follow-up (r=0.319, p=0.03). Additionally, the participants' total number of protracted symptoms was positively correlated with their highest D-dimer levels (r=0.337, p=0.021) and CRP levels during hospitalization (r=0.282, p=0.05).

The duration of their hospitalization was positively correlated with the total number of protracted symptoms (r=0.39, p=0.06), HADS-D scores (r=0.564, p<0.001), and HADS-A scores (r=0.658, p<0.001) during the follow-up.

The number of total symptoms experienced by the participants during hospitalization was positively

correlated with the number of protracted symptoms they experienced during the follow-up ($r=0.675$, $p<0.001$).

A binary logistic regression was performed to predict the existence of a high number of protracted symptoms (more than two symptoms) among the 47 participants during the follow-up. The final model was able to fit the data adequately (Hosmer and Lemeshow's $X^2=8.4$, $p=0.1$) and predicted a higher number of protracted symptoms (omnibus $X2(1)= 27$, $p <0.001$). Overall, the model correctly predicted 87.2% of all cases. The selection of the independent variables for the binary logistic analysis was based on previous correlation analyses. Four predictors were included in the model using the backward LR method (CRP, D-dimer, HADS-D scores during follow-up, and number of total symptoms experienced by the patient during hospitalization). A higher number of symptoms experienced by the patients during acute illness was found to be associated with a higher number of protracted symptoms during the follow-up (OR=1.55, CI 95% 1.21−1.99; squared Wald statistics are displayed in Table 4). The assumptions of linearity and multicollinearity were satisfied.

Table 4. Binary logistic regression results for protracted symptoms during follow-up

	B	**SE**	**Wald**	**p**	**OR**	**95% CI for OR**
Number of total symptoms during acute infection	0.44	0.13	12.1	0.001	1.55	1.21-1.99

OR: odds ratio; CI: confidence interval

A binary logistic regression was performed to predict the probability of considerable depression scores among the 47 participants during the follow-up. The final model was able to fit the data adequately (Hosmer and Lemeshow's $X^2=1.9$, $p=0.9$) and predict considerable depressive symptoms among the participants (Omnibus $X2(1)=26.9$, $p <0.001$). Overall, the model correctly predicted 93.6% of all cases. The selection of the independent variables for the binary logistic analysis was based on previous correlation analyses. Three predictors were included in the model by using the backward LR method (CRP, D-dimer, and number of total protracted symptoms). The participants' highest CRP level during hospitalization was found to be associated with increased odds of depression symptoms during the follow-up (OR=1.09, CI 95% 1.004−1.195). The assumptions of linearity and multicollinearity were satisfied (statistics are presented in Table 5).

Table 5. Binary logistic regression results for depression at sixth month.

	B	**SE**	**Wald**	**p**	**OR**	**95% CI for OR**
CRP	0.09	3.9	4.18	**0.04**	1.09	1.004-1.195

CRP= C-reactive protein; OR: odds ratio; CI:confidence interval

DISCUSSION

The initial objective of the study was to identify long term mental outcomes of COVID-19 survivors treated in hospital. To achieve this, we prospectively investigated psychiatric sequelae and protracted symptoms through a follow-up conducted six months after the discharge of 47 patients who were hospitalized with COVID-19. We observed a significant decrease in their symptoms of depression and anxiety, and insomnia over time, but an exacerbation of their acute stress symptoms. Ongoing depressive symptoms during the follow-up was predicted by systemic inflammation during acute infection. The most frequently reported protracted symptoms during the follow-up were fatigue, abdominal pain, and headaches. A higher number of infectious symptoms during hospitalization predicted a higher number of protracted symptoms during the follow-up.

We observed the prevalence of clinically significant symptoms of anxiety (42%) and depression (19%) during the participants' hospitalization. Half of the

participants also displayed sleep disturbances. A systematic review of psychiatric sequelae of those who recovered from COVID-19 revealed that >30% of the participants in 10 studies presented with anxiety and depression[20]. Whereas several studies compared COVID-19 survivors to patients with other respiratory diseases and found that people who recovered from COVID-19 displayed a substantially higher risk of developing anxiety or depressive symptoms[21,22]. During the follow-up in the present study, only 10% of the participants displayed elevated anxiety symptoms, whereas 12% displayed elevated depressive symptoms and 23.4% reported sleep problems. The participants showed a significant decrease in anxiety, depression, and insomnia over time irrespective of their gender and previous psychiatric history. Anxiety and depression were the psychiatric disturbances most frequently reported by COVID-19 survivors during or soon after their hospitalization[20] Although patients with COVID-19 displayed significantly higher anxiety and depressive symptoms after recovery than those with other respiratory disease infections, most studies revealed that these symptoms generally improved over time[20]. Similarly, a systematic review and meta-analysis of psychiatric presentations during the MERS and SARS crises revealed that the prevalence rates of depression and anxiety among patients decreased during the post-illness phase (12.3% and 10%, respectively)[23].

Several recent studies investigated the effect of inflammatory markers on mental problems in COVID-19 patients. CRP is a biomarker of inflammation that has been shown to be elevated in COVID-19 patients, and depression has been identified as a potential risk factor for severe COVID-19 outcomes[1,24]. Several studies reported that correlation between systemic immune-inflammation index (SII) and anxiety and depression in COVID-19 patients. Moreover, Mazza et. al. concluded that alteration in SII predicted change in depression[24].One study conducted in Spain found that COVID-19 patients with higher CRP levels were more likely to experience depression during hospitalization, with CRP levels being a significant predictor of depressive symptoms even after controlling for age, sex, and disease severity[25]. In line with previous research, our findings suggest that COVID-19 could result in prolonged systemic inflammation for at least up to six months after acute infection, and chronic inflammation could be associated with the persistence of depressive symptoms.

Acute disease severity parameters (illness stage, lowest oxygen saturation level) were not found to be associated with anxiety and depression symptoms during the follow-up. However, only individuals with stage 2 and stage 3 COVID-19 participated in our study. Therefore, we could not assess patients with more severe symptoms. Similarly, Tomasoni et al. reported that neither anxiety nor depression were predicted by clinical parameters or disease severity[4]. In contrast, several studies suggested that disease severity is a risk factor for depression and anxiety[7,21,26]. In the present study, patients with a history of psychiatric conditions suffered more from anxiety and acute stress during their hospitalization. However, their previous psychiatric history did not affect their psychiatric sequelae during the follow-up in our study. This was not in line with the findings of other studies, which indicated that previous psychiatric history predicted anxiety and depression during follow-up assessments[24].

Initially, 59.6% of the participants displayed mild symptoms of acute stress disorder, whereas 17% and 2.1% of them displayed moderate and severe symptoms of acute stress order, respectively. However, these trauma-related symptoms worsened over time, as 38.3%, 36.2%, and 8.5% of the participants displayed mild, moderate, and severe symptoms of acute stress, respectively, during the follow-up. Therefore, at least a third of our participants may be at risk of developing Post Traumatic Stress Disorder (PTSD). The prevalence of PTSD among COVID-19 survivors has been reported to range from 6.5% to 42.8% [20]. A recent meta-analysis found that the estimated prevalence of PTSD during the pandemic was 22.6%[27]. We observed that a family history of COVID-19 was associated with an increased severity of acute stress symptoms among the participants during the follow-up. In several studies, relatives/friends/acquaintances who were infected/hospitalized due to infection were found to be pandemic-related risk factors for PTSD. In addition, women were found to predominantly experience moderate symptoms of acute stress, which is consistent with previous research that found that being female is a risk factor for PTSD during a pandemic[19,27]. Illness severity, which included COVID stage, length of hospitalization, lowest oxygen saturation level, and inflammation parameters during hospitalization, was not found to be associated with severity of trauma-related symptoms during the follow-up. Some follow-up studies

reported an improvement at 1−3 months[24] whereas others did not[28,29]. The variation between results of the studies could be due to differences of tools detected trauma related symptoms and/or different time point which participants' evaluation.

The COVID-19 symptomatology and symptom duration of the infected individuals displayed considerable heterogeneity. During their hospitalization, 20 (42.6%) patients reported experiencing mildly severe symptoms, whereas 27 (57.4%) patients reported experiencing severe symptoms. The most frequently reported physical symptoms during hospitalization were fatigue (100%), myalgia (71%), dyspnea (60%), fever (53.2%), and cough (48%). During the follow-up, 31 (66%) patients reported experiencing mild physical symptoms, whereas 16 (34%) patients reported experiencing moderate physical symptoms. The most frequently reported persistent symptoms were fatigue (76%), abdominal pain (68%), headache (33%). Akin to our results, fatigue was found to be the most prominent symptom among recovering patients[7,30]. Although fatigue reportedly improved over time, it was still found to be elevated in follow-up longitudinal studies[31,320].

The risk factors for persistent symptoms have not been entirely elucidated. The logistic regression analysis in our study showed that experiencing a higher number of infectious symptoms during hospitalization was associated with increased odds of a higher number of protracted symptoms six months later (OR=1.5). Consistent with our results, Sudre et al. recently found that experiencing more than five symptoms during the first week of illness was associated with prolonged COVID (>28 days)[30]. Being a woman, having preexisting psychiatric disorders, being older, and smoking actively, were found to be associated with long-term risk[33].

Recent studies suggest that COVID-19 infection may be associated with disrupted sleep and poor sleep quality[20]. Several authors have reported that COVID-19-positive patients have significantly higher PSQI scores compared to healthy controls. For example, a study conducted by Al-Ameri L.T. et al. suggested that patients who recovered from COVID-19 infection displayed higher total PSQI scores than healthy controls[34]. Moreover, a study conducted in 2022 showed that more severe covid infection caused higher PSQI scores[35]. Another study by Kalamara E. et. al., investigated the long-term sleep effect of COVID-19 infection at three-time points and revealed that except for sleep duration, total and all other subgroup scores decreased at six months after the infection. But none of these changes were statistically significant[36]. In our study, we found a statistically significant improvement in sleep quality. Our results showed that the total score and sub-scores of subjective sleep quality, sleep duration, sleep disturbances, and daytime dysfunction decreased at six months of discharge. Similar to the study of Kalamara E. et. al., our patients displayed persistent symptoms of poor sleep quality. It has been suggested that this association may be due to the physiological effects of the virus on the body, as well as the psychological stress and anxiety associated with the pandemic.

Although the present study presented insightful findings, its limitations must also be considered. First, the sample size was too small to generalize the findings over time. Second, only individuals with stage 2 and stage 3 COVID-19 participated in both assessments in our study. Third, we had low response rate during the follow-up. Last, we could not detect inflammatory markers during the follow-up which could allow us to understand whether the decrease in inflammatory markers could be associated with the decrease in depression symptoms. Further longitudinal studies are needed to explore the interaction between systemic inflammation and depression among COVID-19 patients.

We observed that the symptoms of anxiety and depression, and sleep disturbance experienced by former COVID-19 patients who were treated in a hospital setting improved six months after their discharge. However, their trauma-related symptoms increased over time. We also found that the severity of their inflammation during acute infection is related to protracted depression symptoms even six months after infection. Thus, treatments that target chronic neuroinflammation should be examined as a potential solution in future studies. Many symptoms were found to persist several months after hospitalization for COVID-19. Given that protracted symptoms are associated with markedly increased disability, patients with a high symptom burden during acute illness should be followed more closely.

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