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ORIGINAL ARTICLE

Self-reported anxiety and depression among COVID-19 patients within six months of follow-up: A prospective cohort study

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Abstract

Objective: This prospective cohort study aimed to investigate the prevalence of self-reported moderate or severe anxiety and depression among COVID-19 patients during a six-month follow-up and to identify associated baseline factors.

Methods: The study included patients aged ≥18 years who tested positive for SARS-CoV-2 at Dokuz Eylul University Hospital, Turkey, between November 2020 and May 2021. Telephone interviews were conducted at 1st, 3rd, and 6th months post-diagnosis to assess feelings of anxiety and depression using the EQ-5D-3L scale. Generalized estimating equations were employed to identify factors associated with anxiety and depression after infection.

Results: A total of 5446 patients participated in the study. The prevalence of feeling anxious or depressive at 1st, 3rd, and 6th months post-diagnosis was 18.5%, 17.9%, and 15.4%, respectively. Several factors were associated with self-reported anxiety or depression: Older age (≥65 years; OR: 1.17, 95% CI: 0.95-1.44), female gender (OR: 1.76, 95% CI: 1.58-1.96), unfavourable economic status (OR: 1.62, 95% CI: 1.34-1.97), more symptoms (4-5, OR: 1.48, 95% CI: 1.21-1.81; ≥5, OR: 1.65, 95% CI: 1.35-2.01), having multiple underlying health conditions (1-2, OR: 1.35, 95% CI: 1.19-1.54; ≥3: OR: 1.50, 95% CI: 1.13-1.99), and intensive care unit admission (OR: 2.58, 95% CI: 1.70-3.90).

Conclusion: COVID-19 patients commonly experience anxiety or depression, which may persist long-term. Gender, economic status, and disease severity play significant roles in their psychological well-being. Identifying vulnerable groups can be instrumental in early diagnosis and provision of targeted mental care services.

Keywords: Long COVID, Anxiety, Depression, Cohort Studies

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INTRODUCTION

Stressful events like disasters or outbreaks trigger emotional disorders such as posttraumatic stress disorder (PTSD), major depression, anxiety and sleep disorders [1,2,3]. Previous outbreaks taught that there were psychological impacts as well as biological ones on the infected population [4]. The cohort study that included the patients with severe acute respiratory syndrome coronavirus (SARS-CoV) in Hong Kong has shown that psychiatric disorder prevalence 30 months after diagnosis was 33.3% [2]. The studies about the post-acute stage of MERS (Middle East respiratory syndrome) and SARS indicated that depressive mood, anxiety, euphoria and sleep disorders were the most common complaints among patients [5].

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is a newly emerged infectious disease with higher fatality in certain groups such as people with low immunity and the elderly population [6,7]. Therefore, the pandemic has been an unpredictable stressor for people in medical, social, economic, and cultural contexts.

COVID-19 affected the mental state of populations in various ways [8,9]. In the beginning, the strict restrictions in daily life to prevent the spread of the virus combined with the lack of knowledge about an unknown disease became a threat to the mental well-being of patients who were infected by SARS-CoV-2 [10,11]. Precautions for the pandemic such as lockdowns, self-isolation and compulsory lifestyle changes also affected people's physical and mental health [12,13]. Those containment measures increased feeling lonely, anxious and depressive, alcohol and drug abuse, sleep disorders, self-harm and suicide [14].

Knowledge on post-COVID-19 conditions grew rapidly with an increasing number of studies [15–17]. Studies have supported that SARS-CoV-2 can cause neuropsychiatric symptoms and damage the central nervous system (CNS) directly or indirectly through the immune response mechanism [18–20]. For the acute phase of the disease, neuropsychiatric symptoms such as sleep disorders, concentration deficit, change in appetite, anxiety, somatization, loss of energy and amnesia have been reported in various studies [21–25]. In a meta-analysis, the most common persistent neuropsychological symptoms after 6 months of diagnosis were sleep disorder, anxiety and PTSD [26,27].

Assessing the level of anxiety or depression during the pandemic is important to identify the vulnerable groups for mental health services. EuroQol five-dimension three-level (EQ-5D-3L) is a generic measurement for the quality of life which includes a dimension assessing anxiety and depression. It is useful and efficient to detect anxious and depressive moods [28]. A prospective cohort study in Canada used patient-reported outcome measures and reported that COVID-19 patients had a moderate problem in the anxiety/depression dimension. Patients with higher comorbidities had more anxiety or depression compared to others [29].

There is limited number of studies on a wide group of patients' mental health states after being diagnosed with COVID-19. In this study, we aimed to determine the prevalence and possible baseline determinants of feeling anxious or depressive among the COVID-19 patients within six months of follow-up time.

METHODS

Study Type and Follow-Up Center

This prospective cohort study included participants aged ≥18 years who were diagnosed with COVID-19 between November 1, 2020 and May 31, 2021 in Dokuz Eylul University (DEU) hospital. DEU hospital is a large tertiary care public hospital in Izmir, Turkey. At DEU hospital, COVID-19 Follow-up Center (DEU-COVIMER) was established in January 2021 to monitor the long-term health conditions of COVID-19. Under the supervision of two epidemiology experts, and five public health researchers, five staff have been working in DEU-COVIMER [30].

Data Collection Tools/Methods

At the 1st, 3rd and 6th months after the first positive test date, pre-trained DEU-COVIMER staff called patients by telephone and interviewed using structured questions. Data collection forms were developed after revising the existing guidelines and literature [31,32]observational multisite study. This protocol is linked with the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC. The staff were trained on data collection forms, data registration and basic communication skills at the beginning of the follow-ups. Telephone interviews were standardized using role-play technics with the staff. Prior to starting data collection, we piloted the questionnaire on five COVID-19 healthcare workers. In order to increase the response rate, the staff made at least five attempts until the end of the working hour. All participants provided oral informed consent before starting the telephone interview. Ethics committee approval was obtained from the Dokuz Eylul University Non-Interventional Research Ethical Board (No: 2021/02-66) for the study.

Study Group

Between November 1st, 2020 and May 31th, 2021, a total of 6701 individuals aged ≥18 years were tested positive for SARS-CoV-2 RNA. Figure 1 shows the flowchart of the patients included in the study. Due to DEU-COVIMER becoming fully operational on January 11, 2021; two cohorts were established. The first cohort was November 2020 cohort that the first-month interview was already missed, so they were interviewed in the 3rd and 6th months. The second cohort was December 2020-May 2021 cohort which had been monitored for one, three and six months after the diagnosis. If patients refused to participate at a time point, we excluded them from the next follow-up call. In total 5610 respondents completed the first interview corresponding either in the 1st month or the 3rd month. We also excluded 164 respondents who reported a psychiatric disease in the first interview. In total, data from 5446 people were included in the analysis (Figure 1). The minimum sample size estimated was 1266 assuming a minimum effect size as w=0.10, power=0.90 alpha=0.05 and df=2 using G power [33].

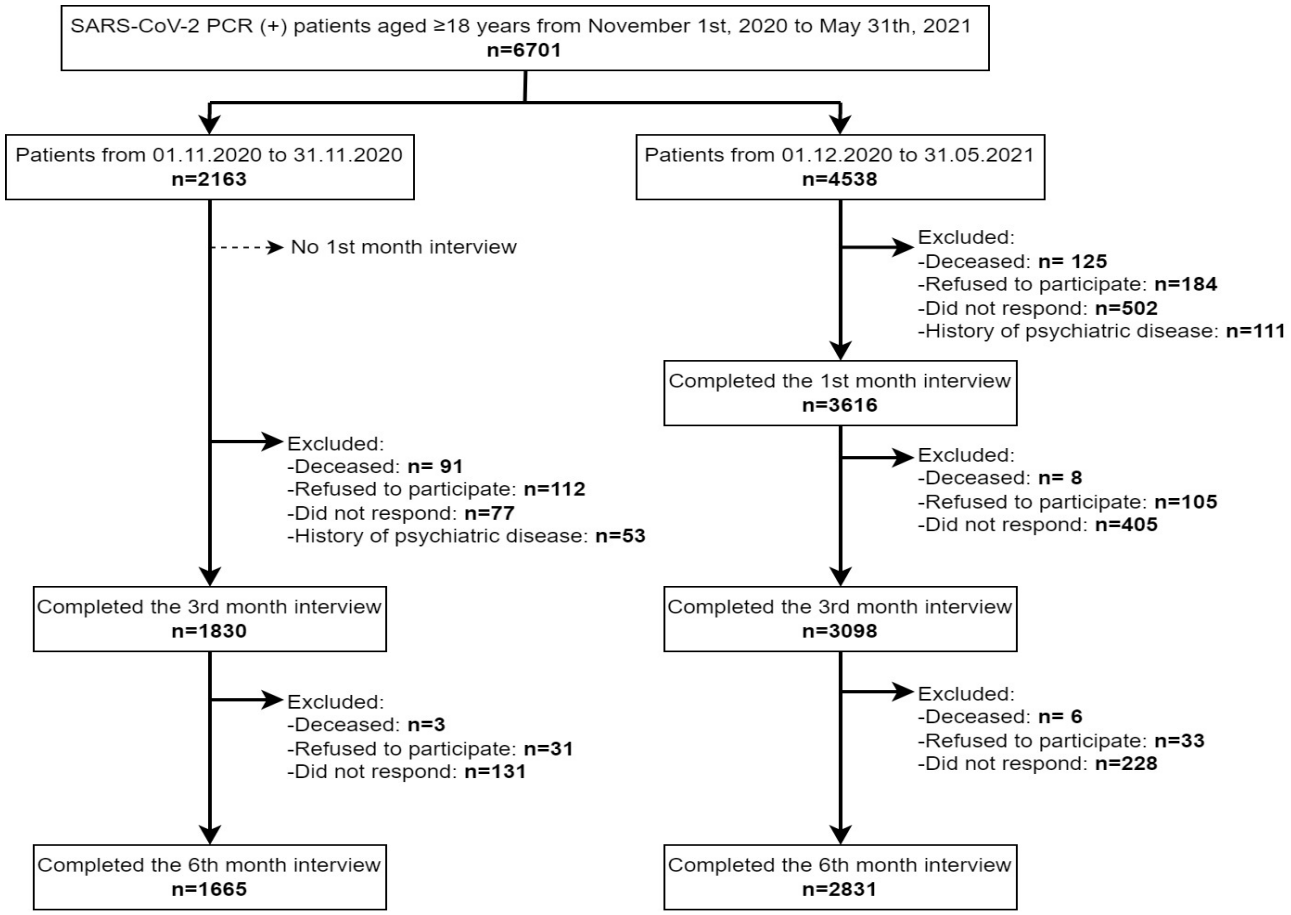

Figure 1: Flowchart of the patients included in this study, DEU Hospital, Izmir, Turkey, November 2020-May 2021

Variables in The Study

The dependent variable of the study was self-reported moderate or severe feeling of anxiety or depression within six months of monitoring according to the EQ-5D-3L general quality of life scale. The EQ-5D-3L is a measurement tool of self-reported health, which gives an opinion about a health state, reflecting the relative importance of different types of health problems. The EQ-5D-3L consists of five dimensions: Mobility, Usual Activities, Self-care, Pain & Discomfort, Anxiety & Depression [34]. The fifth dimension of EQ-5D-3L measures emotional state. EQ-5D reflects the quality of life at the time of application. This questionnaire was administered during 1st, 3rd and 6th month follow-ups. Responses for feeling of anxiety or depression were as follows: "I am not anxious or depressed", "I am moderately anxious or depressed" and "I am extremely anxious or depressed".

To ensure its applicability in different populations, the EQ-5D has been translated and validated in various languages, including Turkish. The EQ-5D was developed and validated into Turkish in 1999. The study included the translation process and validation of the Turkish version of the EQ-5D, as well as the assessment of its psychometric properties. The findings suggest that the Turkish version of the EQ-5D is a reliable and valid tool for measuring health-related quality of life in the Turkish population [35].

Reverse transcriptase-polymerase chain reaction (RT-PCR) test date, age, gender and hospital admission were retrieved from the hospital information system. Educational status,

jobs, perceived economic status, marital status, underlying health conditions and symptoms were patient-reported.

Statistical Analysis

Categorical variables were summarized as numbers and percentages (n, %) and were compared with chi-squared test or Fisher's exact test. The data structure was longitudinal so we used generalized estimating equations (GEE) with a first-order autoregressive AR-1 as the working correlation structure to evaluate reporting moderately/extremely anxiety or depression within six months of follow-up. GEE models are a statistical approach for analyzing longitudinal data, which often exhibit correlation structures due to the repeated measurements taken over time on the same individuals. It allows controlling for the potential confounding effects of correlation. In model 1, separate models were fitted for each explanatory variable with time adjustment. The final multivariate model included all explanatory variables. Estimates were presented as odds ratios with 95% confidence intervals. Data management and analysis were performed with R version 4.0.2 (packages: tidyverse, compareGroups, geepack, sjPlot).

RESULTS

Table 1 presents the general characteristics of the participants. A total of 5446 patients (female: 51.3%, age: 42.9±15.1) followed for a mean of 168 ±47 days after RT-PCR positivity. Among them, 29.6% (n=1613) had underlying health conditions. The most common three underlying health conditions were hypertension (15%), diabetes (10.3%) and coronary artery disease (5.9%), 8.1% of the patients received inpatient care.

The percentages of anxious and depressive feelings were 18.5%, 17.9% and 15.4% on the 1st, 3rd and 6th-month follow-up, respectively. Of the 3616 respondents who completed the 1st month interview, 2.9% (n=106)

Table 1. General characteristics of the COVID-19 patients who agreed to participate in the study

	n	%	n (total)
Age group			5446
18-49 years	3716	68.2	
50-64 years	1205	22.1	
≥65 years	525	9.64	
Female gender	2792	51.3	5446
Education			5412
University	2011	37.2	
High school	1513	28.0	
Secondary school	623	11.5	
Primary school	1058	19.5	
Less than primary school	207	3.82	
Healthcare worker	571	10.5	5446
Perceived economic status			5385
Bad	682	12.7	
Moderate	3625	67.3	
Good	1078	20.0	
Marital status			5412
Married	3613	66.8	
Not married	1799	33.2	
Number of underlying health conditions			5446
None	3833	70.4	
1-2	1436	26.4	
≥3	177	3.2	
Number of symptoms			5446
None	585	10.7	
1-3	2299	42.2	
4-5	1266	23.2	
>5	1296	23.8	
Hospitalization			5446
No	5005	91.9	
Inpatient care service	375	6.9	
Intensive care unit	66	1.2	

reported insomnia, 2.2% reported (n=78) hypersomnia/sleepiness and %1.9 reported (n=70) difficulty in concentrating. For the 3rd month (n=4928) and 6th month (n=4496), percentage of insomnia were 1.3% (n=62) and 0.5% (n=24), respectively while for the hypersomnia/sleepiness, 0.9% (n=43) and 0.5% (n=22), respectively. Difficulty in concentrating were also reported as 0.8% (n=39) and 0.4% (n=39) for 3rd month and 6th month, respectively.

Table 2 shows percentages of reporting moderately/extremely feeling of anxiety or depression at the 1st, 3rd and 6th months. Feeling of anxiety and depression were more common in patients aged ≥65 years (3rd month: 22.2%) and in females (3rd month: 21.7%). Participants with less than secondary school education and those with bad economic status reported more feeling of anxiety or depression. There was a positive relationship between the increase in the total number of symptoms, increase in the number of underlying health conditions and reporting of anxious or depressive feelings. The reported frequency of anxious or depressive feelings in the third month was 39.7% in the ICU survivors.

Table 2. Number and percentages for reporting moderately/extremely feeling of anxiety or depression at the 1st, 3rd and 6th stratified by baseline patient characteristics

	1st month				3rd month				6th month			
	n	Yes n=659	%	p	n	Yes n=876	%	p	n	Yes n=691	%	p
Age group	3555			0.007	4891			<0.001	4493			0.20
18-49 years		428	17.8			551	16.5			453	14.8	
50-64 years		150	18.3			224	20.6			163	15.9	
≥65		81	25.0			101	22.2			75	18.1	
Gender	3555			<0.001	4891			<0.001	4493			<0.001
Male		249	14.6			333	13.9			225	10.2	
Female		410	22.2			543	21.7			466	20.3	
Education	3535			<0.001	4867			0.01	4474			0.008
University		259	19.8			320	17.6			229	13.7	
High school		153	15.3			222	16.3			186	14.8	
Secondary school		63	15.5			89	16.2			81	16.4	
Primary school		144	20.8			194	20.3			153	17.4	
Less than primary school		37	28.0			46	24.2			40	22.3	
Healthcare worker	3555			0.66	4891			0.14	4493			0.99
Yes		65	19.6			105	20.3			74	15.5	
No		594	18.4			771	17.6			617	15.4	

Table 2. (Contiuned) Number and percentages for reporting moderately/extremely feeling of anxiety or depression at the 1st, 3rd and 6th stratified by baseline patient characteristics

	1st month				3rd month				6th month			
	n	Yes n=659	%	p	n	Yes n=876	%	p	n	Yes n=691	%	p
Perceived economic status	3512			0.001	4843			<0.001	4449			0.02
Bad		106	24.3			147	23.8			109	19.3	
Moderate		437	18.6			556	17.1			450	15.0	
Good		113	15.6			168	17.3			125	14.0	
Marital status	3530			0.85	4865			0.80	4468			0.38
Married		431	18.5			589	18.0			457	15.1	
Not married		225	18.8			281	17.7			231	16.1	
Number of underlying health conditions	3555			<0.001	4891			<0.001	4493			<0.001
None		415	16.7			551	16.0			435	13.8	
1-2		217	22.8			284	22.0			225	18.8	
≥3		27	23.1			41	26.6			31	21.2	
Number of initial symptoms	3555			<0.001	4891			<0.001	4493			<0.001
None		56	14.0			88	17.1			52	11.2	
1-3		212	14.6			294	14.3			234	12.3	
4-5		168	20.5			243	21.3			186	17.7	
>5		223	25.2			251	21.3			219	20.4	
Hospitalization	3555			<0.001	4891			<0.001	4493			0.08
No		592	18.2			788	17.5			621	15.0	
Inpatient care service		46	17.8			65	19.3			58	18.6	
Intensive care unit		21	48.8			23	39.7			12	22.6	

Data was presented as row percentages.

Considering the underlying health conditions; anxiety or depression was more common in the patients with coronary artery disease (29.1%), chronic renal failure (35.5%) and rheumatologic disease (31.7%) at the 1st-month follow-up (Supplementary Table 1).

Multivariate GEE model indicated that female gender (aOR: 1.76, 95% CI: 1.58-1.96), bad economic status (vs. good economic status) (aOR: 1.62, 95% CI: 1.34-1.97), reporting ≥3 underlying health conditions (aOR: 1.50, 95% CI: 1.13-1.99), having more than five baseline symptoms (aOR: 1.65, 95% CI: 1.35-2.01) and type of care (vs. no hospitalization) (ICU care, aOR: 2.58, 95% CI: 1.70-3.90) were positively associated with reporting symptoms within six months (Table 3).

Table 3. Results of GEE models showing the adjusted odds ratios of baseline independent variables for reporting feeling of anxiety or depression

	Model 1	Final model
	aOR (95% CI)	aOR (95% CI)
Age group		
18-49 years	ref	ref
50-64 years	1.14 (1.01-1.29)	1.07 (0.93-1.22)
≥65 years	1.42 (1.21-1.68)	1.17 (0.95-1.44)
Gender: female	1.85 (1.67-2.05)	1.76 (1.58-1.96)
Education		
University	ref	ref
High school	0.89 (0.78-1.02)	0.90 (0.79-1.03)
Secondary school	0.93 (0.78-1.11)	0.91 (0.76-1.09)
Primary school	1.18 (1.02-1.35)	0.97 (0.74-1.26)
Less than primary school	1.59 (1.25 2.03)	0.97 (0.74-1.26)
Healthcare worker	1.11 (0.95-1.31)	1.12 (0.94-1.33)
Perceived economic status		
Good	ref	ref
Moderate	1.09 (0.96-1.25)	1.11 (0.97-1.28)
Bad	1.55 (1.30-1.86)	1.62 (1.34-1.97)
Marital status: Not married	1.02 (0.92-1.14)	1.03 (0.92-1.15)
Number of underlying health conditions		
None	ref	ref
1-2	1.46 (1.31-1.64)	1.35 (1.19-1.54)
≥3	1.77 (1.37-2.27)	1.50 (1.13-1.99)
Number of symptoms		
None	ref	ref
1-3	0.97 (0.80-1.17)	0.99 (0.81-1.20)
4-5	1.51 (1.24-1.85)	1.48 (1.21-1.81)
>5	1.73 (1.42-2.10)	1.65 (1.35-2.01)
Hospitalization		
No	ref	ref
Inpatient care service	1.14 (0.94-1.38)	1.00 (0.82-1.23)
Intensive care unit	2.78 (1.89-4.09)	2.58 (1.70-3.90)

In model 1, each explanatory variable was adjusted with time. The final multivariate model includes all variables and time.

DISCUSSION

This study aimed to evaluate the prevalence of anxious and depressive feelings by using EQ-5D-3L scale fifth dimension among COVID-19 patients in six months of follow-up time. One out of six patients had anxious/depressive feelings within six months. The prevalence of feeling anxious/depressive at the 1st and 3rd-month follow-up was similar, however, it was slightly decreased at the 6th-month follow-up. According to studies utilizing EQ5D as a measure of quality of life among COVID-19 survivors, the dimension of anxiety and depression was found to be the second most highly affected dimension, following the dimension of pain and discomfort. [36,37] In a case-control study in Morocco, there was a significant difference in anxiety and depression dimension between COVID-19 survivors and non-COVID-19 group and COVID-19 survivors were mentally negatively effected by the disease. [38]. This study found that older age, female gender, bad economic status, having health conditions, having more than three symptoms at the time of diagnosis and ICU stay were identified as independent risk factors for anxious and depressive feelings.

In a study with a four-month follow-up, anxiety, stress and depression were reported significantly higher in COVID-19 patients than in non-COVID-19 patients [39]. Furthermore, a systematic review showed that depression and anxiety were the most common psychiatric symptoms in COVID-19 patients [40]. Previous studies reported an increased prevalence of anxiety and depression among COVID-19 survivors and these mental health problems may become long-term comorbidity in patients [25,26]. Our study provides qualitative evidence supporting the literature, although it does not conclusively demonstrate the prevalence.

Compared to the pre-pandemic period, rates of anxiety and depression increased in Turkey during the COVID-19 pandemic and women had a greater likelihood of COVID-19 related anxiety and depression than men [41]. A study conducted in Wuhan among COVID-19 patients during the early pandemic era has shown that females were more vulnerable to depression [42]. Consistent with the results in the general population, we found that women diagnosed with COVID-19 were more susceptible to being anxious and having depressive feelings. This may be due to the predisposition of women to anxiety and depression in general [43,44].

As one of the social determinants of health, bad economic status had a negative impact on mental well-being [45]. Also, the COVID-19 pandemic hurt economic security. Both studies in the United Kingdom and Japan have shown that poor economic status and loss of income worsened mental state and increased anxiety and depression in participants [46,47]. Similarly, in this study, having a bad perceived economic status is a risk factor for feeling anxious and depressive. This may be associated with economic insecurity, fear of losing their job because of pandemic restrictions, or disabilities caused by illness.

Our study revealed that having at least four symptoms was associated with feeling anxious/depressive in COVID-19 patients. The severity of the acute phase of COVID-19 disease can be described along with having comorbidities, initial symptoms, and hospitalization [48,49]. Having numerous symptoms may cause psychiatric distress and COVID-19 symptoms like shortness of breath, fever, and headache may provoke anxiety symptoms [50]. Severe

illness and fear of the clinical progression of illness can be related to feeling anxious and depressive.

We found that having at least one underlying health condition and ICU stay were independent risk factors for feeling anxious or depressive. Studies found that patients who were admitted to inpatient care services were at risk for mental disorders [26,51,52]. ICU survivors were prone to having anxiety, depression or post-traumatic disorder (PTSD) [53]. It may be due to consequences of social isolation during the stay, inflammatory process and clinical predictors [22,54].

The study has several strengths. The study has a large sample size. Data from over 6700 patients diagnosed in a public hospital were analyzed. The study population included a wide range of patients, from asymptomatic patients to patients with a heavy clinical condition. The population-based prospective study design increases the generalizability of our findings. The follow-up period is relatively long given that most of the studies in the literature are based on 12 weeks follow up or on a small number of patient groups. [55] However, this study has a few limitations. Data were collected by telephone interviews based on patients' statements. This may have caused recall bias. Although the secretaries were trained and standardized for telephone interviews, interviewer bias is possible in collecting the data. In addition, the study does not present data on patient's clinical or laboratory parameters.

CONCLUSION

In conclusion, feeling of anxiety or depression are common in COVID-19 patients and may persist in the long term. Particularly, these feelings were associated with gender, economic status and disease severity. Determination of vulnerable groups for anxiety and depression after COVID-19 can be helpful for early diagnosis and initiation of mental care services.

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Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

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Ethical Declaration: Approval was obtained from the ethics committee of Dokuz Eylul University (No: 2021/02-66). The procedures used in this study adhere to tenets of the Declaration of Helsinki. Verbal informed consent was obtained prior to the interview.

Author Contribution: Concept: BU, ANE, Design: ANE, BU, CC, NS, Supervising: BU, CC, ANE, Data Collection and Processing: NS, ANE, SK, EBS, OT, AFS, Analysis and/or Interpretation: ANE, BU, Writing: NS, Critical Review: BU, ANE, CC.

Data Sharing Statement: Research data are not shared.

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