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Coronavirus Pandemic

Factors associated with long COVID at a pandemic hospital in Turkey: a prospective observational study with 3-month follow-up

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Abstract

Introduction: The aim of this study was to evaluate the course of the coronavirus disease 2019 (COVID-19) symptoms and identify the prognostic factors in patients who continued to have symptoms for ≥ 3 months. The occurrence of symptoms was compared based on gender.

Methodology: This was a prospective cohort study performed at a tertiary chest hospital in Turkey. The clinical features of patients with COVID-19, health anxiety scores, and the course of symptoms at admission and follow-up were compared based on gender. The primary outcome was the distribution and rate of persistent symptoms at the third month; and the secondary outcomes were the number and distribution of symptoms by gender, and the relationship between symptoms and health anxiety.

Results: A total of 110 patients (mean age of 45 years) were followed. Of these, 53 (48%) patients were females. Forty-seven (43%) patients, including 17 (32%) females, were hospitalized. The number of highly symptomatic patients with mild disease severity (level 2) was significantly higher among females than males ($p = 0.008$). Eighty-one (74%) patients followed had at least 1 symptom persisting at the end of the third month. During the 3-month follow-up, the total number of symptoms and health anxiety scale scores were significantly higher in females ($p = 0.04$ and $p = 0.004$, respectively), especially in females aged < 50 years ($p = 0.005$).

Conclusions: Thus, persistent symptoms remained at a high rate at 3 months post-COVID; and gender and neuro-psychiatric factors should be discussed in the etiology of long COVID.

Key words: anxiety; coronavirus; gender; symptom; SARS-CoV-2.

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Introduction

The entire world has been affected by the coronavirus disease 2019 (COVID-19) since 31 December 2019. The International Committee on Taxonomy of Viruses designated the virus that causes COVID-19 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 originated in China, and it spread to the entire world within 2.5 months. The World Health Organization (WHO) declared COVID-19 as an "international public health emergency" on 30 January 2020, and a "pandemic" on 11 March 2020. The first COVID-19 case was reported in Turkey on 11 March 2020. As of 25 March 2024, 102,000 deaths and 17.2 million confirmed cases of COVID-19 were reported to WHO from Turkey. Worldwide, there have been 774 million confirmed cases of COVID-19 and 7 million deaths, as of 23 March 2024. At the same time, 13 million vaccine doses were administered globally [1,2].

COVID-19 can affect almost every system in the body and has a wide clinical spectrum, ranging from asymptomatic or mild illness to life-threatening acute respiratory distress syndrome (ARDS). COVID-19 has been reported to have a more severe and fatal course in men, elderly, obese, and those with comorbidities [3].

WHO declared the end of the COVID-19 pandemic in May 2023. However, clinical management of COVID-19 did not seem to end with the diagnosis and treatment of the acute illness. Different terminologies have been used in the literature — such as “post-COVID-19” and “long COVID” — for symptoms that persist after SARS-CoV-2 infection [4]. “Long COVID” has been defined as symptoms that persist usually 3 months after the onset of probable or confirmed SARS-CoV-2 infection and that cannot be explained by an alternative diagnosis. Common long COVID symptoms are fatigue, shortness of breath, and cognitive dysfunction. Symptoms may persist after acute infection or reappear after recovery [1]. Although persistent symptoms after infection have been reported in approximately 10–20% of patients by WHO, rates of up to 93% have been reported in studies [5–11]. There are also studies that have reported long COVID symptoms for up to 2 years [7,12,13]. Age, female gender, obesity, severe illness, duration of illness, lack of vaccine, original SARS-CoV-2 virus or alpha variant, and psychiatric morbidities have been found to be associated with long COVID [7,9,12–16].

Despite several studies on long COVID, the prevalence, causes, duration, and severity of long COVID remain unclear. The characteristics of long COVID may vary depending on age group, gender, underlying comorbidity, disease severity, mental health of individuals, and even their socio-cultural levels. Longitudinal studies targeting populations with certain phenotypes (such as chronic obstructive pulmonary disease, COPD, patients; patients with depression; patients in rural areas; young patients; elderly patients; women; etc) are needed to examine all aspects of the causes of long COVID symptoms.

In our study, we aimed to evaluate the course of symptoms in patients with COVID-19 who reported persistent symptoms for 3 months. The aim was to reveal the association of these symptoms with health anxiety and gender.

Methodology

Study design and participants

This is a prospective cohort study performed in a tertiary chest hospital in an urban area in Turkey. The study was performed between August 2020 and November 2020, and was approved by the ethics committee of the Yedikule Chest Diseases and Thoracic Surgery Research and Training Hospital (Approval number: 06.08.2020/2020-02). Patients who presented to the dedicated COVID-19 outpatient clinics at the same center were consecutively included in the study.

The inclusion criteria were: (1) patients aged over 18 years who presented to the polyclinic with persistent symptoms after the completion of their isolation period; (2) patients with SARS-CoV-2 infection, confirmed using reverse transcriptase polymerase chain reaction (RT-PCR) on nasopharyngeal swabs; and (3) patients who were recommended for isolation and treatment based on their contact history, clinical-laboratory and radiologic findings, and COVID-19 infection.

Individuals who did not meet the above criteria, had a known active infection other than COVID-19-related infection, defined dementia, psychiatric disease, medication use, active malignancy, and those who were illiterate and did not provide informed consent, were excluded from the study. All included patients provided verbal and written informed consent.

Procedures and data collection

A total of 110 patients were included in the study and the medical records were examined. Additional diseases were classified using the Charlson Comorbidity Index (CCI) [17].

COVID-19 disease severity in the patients was determined with a 7-level scale. Levels 1–2 were classified as 'mild disease,' and levels 3–6 as 'moderate–severe disease' [18]. The patients were also categorized into the flowing groups: (1) non-hospitalized, able to perform normal activities; (2) non-hospitalized, unable to perform normal activities but follow-up at home; (3) hospitalized, without oxygen need; (4) hospitalized, with oxygen need; (5) hospitalized, requiring high-flow nasal oxygen (HFNO) or non-invasive mechanical ventilation (NIMV); (6) hospitalized, requiring extracorporeal membrane oxygenation (ECMO) and/or invasive mechanical ventilation (IMV); (7) hospitalized, death.

Contact numbers of the patients were obtained for follow-ups at regular intervals. Fifteen 'standard' COVID-19-related symptoms were recorded at the time of diagnosis; and were inquired and recorded at the first, second, and third month follow-ups. These symptoms were categorized into four groups: (1) systemic symptoms which included fever, myalgia, arthralgia, fatigue, and anorexia; (2) respiratory-cardiovascular symptoms which included cough-sputum, nasal symptoms, sore throat, dyspnea, chest pain, and palpitation; (3) gastrointestinal symptoms which included abdominal pain, nausea-vomiting, and diarrhea; and (4) neurological symptoms which included headache, and anosmia-dysgeusia.

Clinical findings and complications that were previously not present but occurred during the follow-up were categorized into seven groups: (1) respiratory complications such as pulmonary embolism, bronchial hyperreactivity, hemoptysis, and secondary pulmonary infection; (2) cardiovascular complications such as arrhythmia, tachycardia, and hypertension; (3) renal dysfunction when the values of blood urea nitrogen (BUN) and creatine were above the normal laboratory range; (4) liver dysfunction when the values for alanine transaminase (ALT) and aspartate transaminase (AST) were above the normal laboratory range; (5) hyperglycemia, including newly diagnosed diabetes mellitus; (6) eye symptoms such as conjunctivitis and vision loss; (7) neuropsychiatric findings such as anxiety, panic attack, sleep disorders, and attention-memory disorders.

The patients' laboratory values and radiologic images were recorded both at the time of diagnosis and in the first month. Follow-ups were discontinued three months after diagnosis. At the conclusion of the study period, the total number of symptoms in each patient; and the number of symptoms at the time of diagnosis, and at the first, second, and third month were calculated.

The patients were asked to complete a "health anxiety scale form" during their first presentation at the hospital. The health anxiety questionnaire (HAQ) is a survey developed by Salkovskis *et al*. to determine individuals' levels of anxiety about their health [19]. The validity and reliability of this self-report scale for the Turkish community was established by Aydemir *et al.* [20]. The questionnaire consisted of 18 questions with four response options each. The total score ranged from 0 to 54, and a higher total score indicated increased health anxiety.

Outcomes

The primary outcome of our study was the distribution and rate of persistent symptoms at the third month in patients diagnosed with COVID-19. The secondary outcomes were the number and distribution of symptoms by gender, and the relationship between symptoms and health anxiety.

Statistical analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corp, Armonk, NY, USA). The data was checked for suitability for normal distribution using the Shapiro-Wilk test. Categorical variables were presented as counts and percentages. Continuous variables were presented as mean and standard deviation (SD), and compared using the independent sample t-test if normally distributed; otherwise, the median and interquartile range (IQR) was used to present the data, and the Mann-Whitney U test was used for comparison. The Chi-square test was used to compare categorical data. p values of < 0.05 indicated that the difference was statistically significant.

Results

A total of 110 patients with a mean age of 45.1 years were included in the study. The patients' demographic data, disease severity, number of symptoms, health anxiety, complications, and laboratory data were compared, in consideration of gender.

Fifty-three (48.1%) patients were female and fewer females smoked in comparison with males (24.5% vs 64.9%; $p < 0.001$). A total of 47 patients (42.7%) were hospitalized; 17 (32%) of these were female and 30 were male (52.6%). Although male patients displayed a higher rate of hospitalization, there was no statistical difference in the hospitalization of females vs males (32% vs. 50.9%, $p = 0.07$).

Seventy-nine of the 110 patients (71.8%) had at least one comorbidity. The most common comorbidities were hypertension (26.4%), followed by diabetes mellitus (17.3%), asthma and COPD (15.5%), and cardiovascular disease (11.8%). CCI was similar for males and females ($p = 0.48$). The initial thoracic computed tomography (CT) of 82 patients (74.5%) showed involvement. Health anxiety scale scores were significantly higher in female patients compared with males (22 (14–28) vs. 16 (10.2–21.7), $p = 0.004$). Male and female patients were similar in terms of age, body mass index (BMI), CCI, time from symptom onset to presentation, thoracic involvement in initial thoracic CT, and hospitalization ($p > 0.05$) (Table 1).

According to the disease severity classification, 63 patients (57.3%) had mild disease severity (level 1–2). There was a significant difference ($p = 0.008$) between the female and male patients in terms of disease

Table 1. Comparison of demographics, and radiological and clinical status of female and male patients.

Characteristics	Female (n = 53)	Male (n = 57)	*p* value
Age, years (mean ± SD)	45.3 ± 13.9	44.8 ± 15.1	0.84
Smoker patients, n (%)	13 (24.5)	37 (64.9)	0.001*
BMI (mean ± SD)	27.6 ± 4.9	27.0 ± 3.5	0.5
Comorbidities, n (%)			
Diabetes mellitus	9 (17)	10 (17.5)	1.00
Hypertension	14 (26.4)	15 (26.3)	1.00
Cardiovascular disease	3 (5.7)	10 (17.5)	0.07
Thyroid disease	6 (11.3)	3 (5.3)	0.30
COPD	0 (0)	3 (5.3)	0.24
Asthma	7 (13.2)	7 (13.2)	1.00
Malignity	2 (3.8)	1 (1.8)	0.68
CCI, median (IQR)	1 (0-2)	1 (0-3)	0.48
Thoracic involvement on baseline CT scan, n (%)	40 (77.4)	42 (73.7)	0.66
Hospitalized, n (%)	17(32)	30 (52.6)	0.07
HAQ score, median (IQR)	22 (14-28)	16 (10.2-21.7)	0.004*

BMI: body mass index; CCI: Charlson comorbidity index; COPD: chronic obstructive lung disease; CT: computed tomography; HAQ: health anxiety questionnaire; IQR: interquartile range; SD: standard deviation. * Statistically significant.

severity, and this difference resulted from level 2 patients (non-hospitalized, unable to perform normal activities, very symptomatic). The majority of patients were level 2 (43 patients, 39.1%) and the number of females in this group was significantly higher than males (30 (56.6%) vs 13 (22.8%)). Although level 1 (non-hospitalized, able to perform normal activities, less symptomatic) and level 3–6 (moderate-severe disease severity) patient groups included more males, there was no significant difference ($p > 0.05$) (Table 2). The most common symptoms reported at the time of diagnosis were fatigue (89.1%), myalgia-arthralgia (79.1%), and cough-sputum (72.7%). Less frequent symptoms were headache (65.5%), anorexia (62.7%), dyspnea (59.1%), fever (59.1%), anosmia-dysgeusia (57.3%), chest pain (51.8%), sore throat (50.9%), nasal symptoms (42.7%), diarrhea (42.7%), abdominal pain (38.2%), nausea-vomiting (37.3%), and palpitations (35.5%). When we divided the symptoms into subgroups according to the relevant system (systemic, cardiopulmonary, gastrointestinal, neurological), we found no difference in the types or number of symptoms between the genders ($p > 0.05$).

There was no significant difference between males and females in terms of the median number of symptoms ($p > 0.05$) at the time of diagnosis and the first and third month follow-up. Only 3 patients (2.7%) had no symptoms after 1 month, and 29 patients (26.4%) had no symptoms after 3 months. Of these 29 patients, 12 were females (22.6%), 17 were males (29.8%), and again, there was no significant difference ($p = 0.51$).

However, during the 3-month follow-up, the median (IQR) of total number of symptoms was 20 (15–24.5) in females and 17 (10–23) in males; thus, the number of symptoms was significantly higher in females ($p = 0.04$). At the end of the third month, 81 (73.6%) patients were still symptomatic and their persisting symptoms were, in order of frequency, fatigue (63.0%), dyspnea (54.3%), chest pain (45.7%), cough-sputum (40.7%), palpitation (23.5%), headache (18.5%), myalgia (17.3%), nasal symptoms (16.0%), abdominal pain (14.0%), anorexia (8.6%), nausea-vomiting (7.4%), anosmia-dysgeusia (6.2%), sore throat (2.5%), and diarrhea (2.5%) (Table 2).

Figures 1 and 2 show the distribution of the number of symptoms in females and males at the time of diagnosis, and in the first and third months.

Figure 1. Distribution of the number of symptoms at the time of diagnosis, and in the first and third months in female patients.

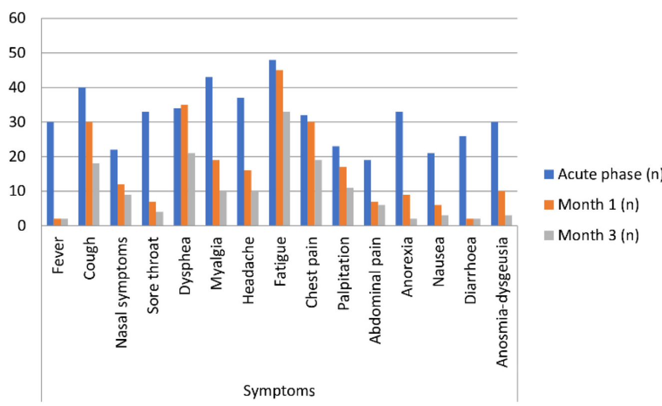

Figure 2. Distribution of the number of symptoms at the time of diagnosis and in the first and third months in male patients.

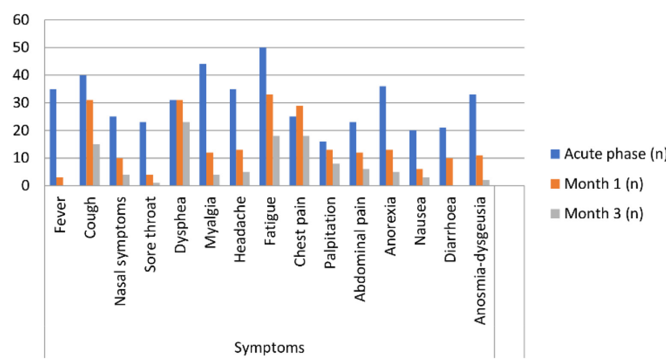

Table 2. Comparison of disease severity and symptom scores of female and male patients.

	Female (n = 53)	Male (n = 57)	*p* value
Severity Level, n (%)			**0.008*†**
Level 1	6 (11.3)	14 (24.6)	
Level 2	30 (56.6)	13 (22.8)	
Level 3	7 (13.2)	9 (15.8)	
Level 4	8 (15.1)	13 (22.8)	
Level 5	2 (3.8)	5 (8.8)	
Level 6	0 (0)	3 (5.3)	
Symptom scores			
Symptom score at admission, median (IQR)	9 (7–11)	8 (5.5–11)	0.12
Symptom score at 1st month, median (IQR)	5 (3–6)	4(2–6)	0.15
Symptom score at 3rd month, median (IQR)	2 (1–4)	1 (0–3.5)	0.1
Total symptom score, median (IQR)	20 (15–24.5)	17 (10–23)	0.04*
Patients without any symptoms at 3rd month, n (%)	12 (22.6)	17 (29.8)	0.51

* Statistically significant; † significance due to patients with level 2.

Table 3. Comparison of complications of female and male patients.

Complications	Female (n = 53)	Male (n = 57)	*p value*
Patients with at least one complication, n (%)	32 (60.4)	34 (59.6)	1.00
Pulmonary complications, n %)	16 (30.2)	22 (38.6)	0.42
Bronchial hyperreactivity, n (%)	13 (24.5)	10 (17.5)	0.48
Secondary pulmonary infections, n (%)	4 (7.5)	10 (17.5)	0.15
Pulmonary embolism, n (%)	2 (3.8)	5 (8.8)	0.44
Hemoptysis, n (%)	0 (0)	1 (1.8)	1.0
Patients with elevated liver enzymes, n (%)	10 (18.9)	17 (29.8)	0.19
Neuropsychiatric involvement, n (%)	12 (22.6)	7 (12.2)	0.2
Visual disturbances, n (%)	3 (5.7)	4 (7)	1.0
Cardiovascular involvement, n (%)	1 (1.9)	5 (8.8)	0.2
Renal involvement, n (%)	0 (0)	3 (5.3)	0.24
Hyperglycemia, n (%)	0 (0)	2 (3.5)	0.46

Considering the laboratory parameters, C-reactive protein (CRP), D-dimer, neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio (NLR) were similar in both groups ($p > 0.05$). However, the male patients had higher BUN, AST, ALT, lactate dehydrogenase (LDH), and ferritin ($p = 0.04$, $p = 0.002$, $p < 0.001$, $p = 0.02$, and $p < 0.001$, respectively); but lower albumin ($p = 0.02$). Differences in values other than LDH and ferritin were not clinically significant.

We observed a total of 109 complications in 110 patients. Pulmonary complications constituted 41.3% of these. At least 1 complication was seen in 66 patients (60%). Females and males were similar in terms of complications during follow-up (60.4%, 59.6%; $p = 0.999$). No mortality was observed in any patient during follow-up (Table 3).

We also divided the patients into two groups based on their age: patients aged < 50 years and patients aged ≥ 50 years; and then formed sub-groups of females and males. We compared male and female patients in these sub-groups in terms of total symptom numbers, health anxiety scores, hospitalization, CCI, and initial radiologic involvement. Health anxiety scores were significantly higher in females aged < 50 years ($p = 0.005$). A comparison of other parameters revealed no significant differences ($p > 0.05$; Table 4).

Discussion

In our study, 81 of 110 patients followed during the post-COVID period had at least one persisting symptom at the end of the third month. The most common symptoms in the third month were fatigue (63.0%), dyspnea (54.3%), and chest pain (45.7%). The most common symptom among the women in the third month was weakness-fatigue, while the most common symptom among the men in the third month was dyspnea. The females tended to report more symptoms, and this may be associated with the higher health anxiety scores among females.

Studies have evaluated persistent symptoms and sequelae at 6-month follow-ups [5,6,21,22], 1-year follow-ups [12,13,23–26], and 2-year follow-ups [7]. However, few studies have examined differences in symptoms based on age and gender, and identified persistent symptoms after the acute disease [8,9,27].

Follow-up studies with individuals recovering from acute COVID-19 infection have reported persistent findings at rates ranging from 40% to 93% [5,6,22,27]. This wide variation in results may be due to differences in age, gender, disease severity, follow-up duration, and clinical evaluation; and therefore, interpreting the results becomes a challenge. At the same time, studies describing the prevalence, causes, and findings of long COVID are mostly cross-sectional and observational studies, that have selection and reporter bias which makes generalization difficult [28]. A comprehensive review included 54 studies that addressed the potential underlying mechanisms of long COVID symptoms. The authors reported that 34 articles speculated on these mechanisms and that the studies were heterogeneous in terms of inclusion criteria [29].

Table 4. Comparison of female and male individuals in sub-groups of patients ≥ 50 years and < 50 years of age.

	Patients (< 50 years of age) (n = 65)			Patients (≥ 50 years of age) (n = 45)		
	Female (n = 33)	Male (n = 32)	*p* value	Female (n = 20)	Male (n = 25)	*p* value
Total symptom score (mean ± SD)	19.7 ± 6.9	17.5 ± 7.1	0.24	19.6 ± 6.9	15.8 ± 7.5	0.09
HAQ score, median (IQR)	25 (15–30.5)	16 (11–20)	0.005*	16.5 (14–26.7)	18 (9.2–23.5)	0.37
Hospitalization n (%)	6 (18.1)	12 (37.5)	0.18	11(55)	18(72)	0.34
CCI, median (IQR)	0 (0–1)	0 (0–1)	0.89	2.5 (1.25–4.0)	3 (2–4)	0.63
Thoracic involvement on baseline CT scan, n (%)	22 (66.7)	18 (56.3)	0.45	19 (95)	24 (96)	1.00

CCI: Charlson comorbidity index; CT: computed tomography; HAQ: health anxiety questionnaire; IQR: interquartile range; SD: standard deviation. * Statistically significant.

Although the proposed definition of long COVID includes the symptoms that persist after SARS-CoV-2 infection and various mechanisms have been described, not all reported symptoms may be caused by SARS-CoV-2 infection [30,31], and some symptoms may be ascribed to SARS-CoV-2 despite having other causes. In a study that included a large French cohort, the authors emphasized that the persistent physical symptoms observed after COVID-19 infection were quite common in the general population, and may be more related to the belief of being infected with SARS-CoV-2; and therefore, a comprehensive medical evaluation was required [32]. In another study, the authors reported that cognitive deficits, one of the symptoms of long COVID, were associated with various symptoms (mood swings and fatigue) and that more than one factor underly them. They emphasized that the long-term effects and clinical significance of these deficiencies were unclear [16].

Some studies reported disease severity as a risk factor for prolonged symptoms [22,27]. However, a puzzling feature of COVID-19 is the observation of prolonged symptoms with all levels of disease severity. Studies also reported that symptoms such as cough, fatigue, chest pain, and anxiety may persist in the long term, even in patients experiencing mild COVID-19 [6,10,14]. In a study that included 269 patients, including 65.7% with severe disease, the participants were followed for 10–14 weeks, and 141 patients (50.9%) demonstrated post-COVID syndrome (at least 1 symptom or radiologic or spirometric change). In this study, the rate of severe disease was high, and it was reported that most of the post-COVID symptoms were mild, and radiologic and spirometric changes were mild and observed in less than 25% of patients [5]. In another study, it was reported that long COVID symptoms continued even in those who had mild COVID-19 with improved pulmonary, radiologic, and functional examinations [6,11]. A study reported that cognitive functions and neuropsychiatric status were affected in patients with mild and moderate COVID-19, and that there was no relationship between cognitive disorders and disease severity [33]. Moreover, many studies reported no relationship between initial disease severity and long COVID [10,14]. The pathophysiologic mechanisms related to the cause of this condition are not clear.

In our study, 47 (42.7%) out of 110 patients were hospitalized. Despite the relatively high number of patients with mild disease severity (level 1–2, 57.3%), the number of patients with persistent symptoms in the third month was high (73.6%). This indicated that, consistent with the literature, patients with moderate–severe disease severity, as well as patients with mild severity, demonstrated prolonged symptoms [6,14,26].

However, it is unclear whether the reported rates of persistent post-COVID-19 symptoms were being reported as higher than the actual rates? We know that COVID-19, beyond being an infectious disease, has also impacted millions of individuals as a powerful stressor. Exposure to intense and long-term stress leads to stress-related psychiatric disorders such as post-traumatic stress disorder (PTSD), anxiety disorder, panic disorder, and depression; in addition to triggering of previous mental disorders. These psychological disorders are more common in females than in males. It is possible, that among the post-COVID-19 patients who were being followed-up, apart from organic reasons and physical stress, social and economic pressure due to the pandemic conditions may have also resulted in these symptoms. Healthcare professionals must make this distinction [14,21].

In related studies, psychiatric morbidities such as PTSD, anxiety/depression, and sleep-memory problems were reported to occur at a rate of 30% to 52.4%, following coronavirus infection. Moreover, the concerned psychiatric morbidities were found to be associated with ongoing physical symptoms [10,34–36]. A study conducted in Turkey included 284 patients, and 86.1% had mild and moderate clinical severity. Among the patients, 38.8% reported impaired sleep quality, 25.4% had PTSD, 18.8% depression, 18.4% anxiety, and 15% had concentration difficulties. The study concluded that PTSD symptom severity was the only independent predictor of prolonged symptoms [14].

In our study, 73 of 110 patients (66.4%) had at least one comorbidity. Those with defined dementia, psychiatric illness, and drug use were not included in the study. It has been reported in the literature that comorbidities may be the cause of long COVID, but we found no relationship between them in our study ($p < 0.05$) [30]. Existing comorbidities may contribute to anxiety, and thus to the number of symptoms; however, comorbidities were found to be similar in males and females in our study ($p = 0.48$).

A longitudinal cohort study conducted over two years included 1192 patients; the rate of patients with at least 1 persistent symptom in the sixth month was 68%, and at the end of the second year this rate was 55%. The authors reported that fatigue and muscle weakness (30%), and difficulty sleeping (25%) were the most to persistent symptoms [7].

In our study, the symptoms of none of our patients were proven in objective tests. In the acute phase, the most common symptoms were fatigue (89.1%), myalgia-arthralgia (79.1%), and cough-sputum (72.7%). In the third month, the most common symptoms were fatigue (63.0%), dyspnea (54.3%), and chest pain (45.7%). However, in the third month, the most common symptom reported by the women was weakness-fatigue, while the most common symptom among the men was dyspnea. This can be explained by the higher number of men with moderate to severe disease. On the other hand, during the follow-up, only 8 (7.3%) patients had to be re-hospitalized, and no mortality occurred. Despite the higher number of female patients than males with at least 1 symptom at the end of the third month, there was no significant difference between the genders. This may be due to the small number of patients included in our study. However, it was also interesting that those female patients had a significantly higher total number of symptoms and health anxiety scores than males (p = 0.04 and 0.004, respectively).

A multi-center cohort study specifically investigating gender differences reported that symptoms of COVID-19 at hospital admission were similar in males and females, but females were more prone to develop post-COVID symptomatology 8 months after hospital discharge than males [9]. In a study with a 1-year follow-up period, the authors reported that women reported more symptoms, suffered more from anxiety and depression, and were less likely to return to work [37]. Consistent with the results of this study, 3 multicenter studies also reported that female gender is a potential risk factor for some post-COVID symptoms, such as fatigue, forgetfulness, dyspnea, and dermatological symptoms [8,12,22].

One noteworthy observation from our study was that the males were in the mild disease severity and the less symptomatic patient group (level 1), and the females were in the mild disease severity and the very symptomatic patient group (level 2). In addition, females were more symptomatic among the outpatients. Therefore, based on the differences between the genders, we conclude that females tend to report more symptoms, and this may be associated with higher health anxiety. We believe that there may be many factors such as health anxiety and gender, that cause persistent symptoms, and additional studies should be conducted to understand these factors.

Health anxiety is defined as worry and fear about having a serious illness. Specifically, pre-existing “health anxiety” may cause individuals to develop more symptoms in stressful conditions such as a pandemic [38]. The short health anxiety inventory (SHAI) was used in a study performed to assess pathologic health anxiety in patients who consulted different specialties during normal times, even outside of the situations that affect a large part of the society such as a pandemic; and 20% of the patients were reported to have health anxiety [39]. It has also been reported in other studies that health anxiety causes increased symptoms and is found at higher levels in women and young individuals [40,41]. Increased health anxiety may also be associated with inappropriate use of healthcare services. In a longitudinal cohort study that reported 2-year follow-up results, long COVID symptoms were associated with decreased health-related quality of life, decreased exercise capacity, psychological abnormality, and increased use of healthcare services after discharge [7].

In our study, the first month laboratory test data were recorded, and none of the parameters could predict long COVID. However, ferritin and LDH values were significantly higher in males compared to females. High peripheral blood biomarkers persisting after recovery from acute infection may be associated with true long COVID. Studies with large patient groups are needed to determine this association.

In our study, 66 (60%) patients had at least one complication. The most common complications were pulmonary complications (n = 38; 34.5%), as was also observed in previous studies [13,24]. Nevertheless, although the males and females were similar in terms of symptoms, females demonstrated more neuropsychiatric symptoms (22.6%, 12.2%; p = 0.2), but other complications were higher in males. This may also explain the more severe disease severity in men and the higher tendency among women to report symptoms.

In a study of 236,379 patients with COVID-19, approximately one-third of the patients had a neurological-psychiatric condition (e.g. stroke, dementia, sleep disorders, anxiety, and mood disorders) during the 6-month follow-up period [21]. In a prospective cohort study, 50.0% of patients had at least one COVID-19-related symptom after 6 months from acute COVID-19 infection, and 48% of patients had at least one COVID-19-related symptom after 12 months. After 12 months, the most common symptoms were amnesia (24.1%), insomnia (14.7%), fatigue (13.5%), and anxiety (12.9%). The authors reported that neuropsychiatric symptoms were the main COVID-19-related symptoms 12 months after acute COVID-19 infection, and these symptoms reduced the quality of life [25]. In a meta-analysis that included 17 studies conducted during the 2.5 years of the pandemic, the long COVID rate was 28%, and 58% of them were in women. 'Brain fog', which came to the fore with COVID-19, is not a medical term, but a term that covers symptoms such as feeling of confusion, forgetfulness, poor concentration, and mental fatigue. In this study, the combined prevalence of mental health conditions and brain fog was reported as 20.4%. A study reported that both brain fog and mental changes showed an increasing prevalence in long COVID over time, and that the prevalence of brain fog was inversely proportional to vaccination rates [42]. In the same study, the authors commented that long COVID symptoms may be reactive to a long-term illness or a separate chronic condition clustered with depression and anxiety [42].

In several studies, neuropsychiatric symptoms came to the fore as the time after acute infection got longer. It is controversial whether these symptoms, defined as long COVID, actually occur due to virus-related causes, and an update to the definition of 'long COVID' should be considered.

In our study, 19 (17.3%) patients demonstrated neuropsychiatric findings, which was a lower rate compared with that reported in the existing literature [23,35,36]. We may have been inadequate in terms of the diagnosis and referral of this group of patients because our hospital was a specialized facility and the relevant branch consultations could not be performed adequately.

In our study, health anxiety scores were significantly higher in females aged < 50 years (p = 0.005); but this difference was not observed in females ≥ 50 years (p = 0.37). Some studies report that anxiety and health anxiety are more frequent in young adults than in the elderly, and more frequent in females than in males [41,43–45]. These observations are similar to the conclusions from our study.

Accurate identification of the vulnerable population is crucial during the acute phase of the disease and in the post-COVID period. Furthermore, it is also important that physicians identify patients with increased symptoms due to mental-social-health anxiety and plan appropriate joint approaches for follow-up. Therefore, it will be useful to conduct studies targeting populations with certain phenotypes to unravel the post-COVID period.

Limitations

This study has several limitations including its single-center design; relatively lower number of patients included which made it difficult to detect small associations; patients' possible undetected pre-COVID abnormalities; absence of pulmonary function test, diffusing capacity of the lung for carbon monoxide (DLCO), and cardiac imaging that would provide objective identification; and the absence of specialist evaluation, especially by neurology and psychiatry specialists.

Conclusions

Uncertainties remain about how long COVID findings persist, and which symptoms occur due to virus-related causes. Despite its limitations, this study demonstrated that persistent symptoms remain at a high rate at 3 months post-COVID, and that gender and neuro-psychiatric factors should be discussed in the etiology of long COVID. However, our results are only indicative due to the small study population; larger studies are needed for definitive results.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles and was approved by the Ethics Committee of Yedikule Chest Diseases and Thoracic Surgery Research and Training Hospital, University of Health Sciences, Istanbul, Turkey (approval number: 06.08.2020/ 2020-02).

Authors' contributions

Chief investigator: BAB; material preparation, data collection, and analysis: BAB, CS; statistical analysis: CS. Both authors contributed to the planning, execution, and completion of the trial. Both authors read and approved the final manuscript.

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Conflict of interests

No conflict of interests is declared.

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