ORIGINAL RESEARCH

Fatigue has a prominent impact on health lasting 12-weeks after COVID-19 infection

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Abstract

Background

While the amount of information on many issues related to COVID-19 has increased, the long-term consequences of illness and disability remain largely unclear. In previous studies on COVID-19 infections, long-lasting functional and symptomatic abnormalities have also been shown. It is predicted that survivors of COVID-19 may have to deal with physical or psychological problems later.

Aim

We aimed to evaluate long-lasting symptoms including fatigue and investigate the associated risk factors.

Methods

In this prospective cohort study, 132 consecutive COVID-19 patients who were previously diagnosed and admitted 13±1 weeks after diagnosis were included. The Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale, the Beck Anxiety Inventory, the Beck Depression Inventory, and the Lawton Instrumental Activities of Daily Living (IADL) Scale were applied in the follow-up visit.

Results

The median age of the patients (76 male, 56 female) was 52. Eighty (61%) of the patients were hospitalized, while 52 (39%) of them were not hospitalized. At least one symptom persisted in 103 (78%) patients, with fatigue (n=48, 36%) being the most common symptom. Both dyspnea and fatigue were more prominent in women than in men (34% vs. 11%, p=0.001 and 46% vs 29%, p=0.03; respectively). Persisted symptoms including fatigue were not significantly associated with hospitalization status. The FACIT scores of the patients at 12 weeks were positively associated with their depression and anxiety levels (R: 0.55, p=0.0001 and R: 0.42, p=0.0001), while they were negatively associated with their IADL scores (R: -0.25, p=0.004).

Conclusions

Fatigue was the most frequent persistent symptom. The initial fatigue scores were higher in the severely ill patients. Persistent fatigue was not associated with disease severity but was closely associated with anxiety and depression.

Keywords: COVID-19, pandemic, fatigue, persistent symptoms, risk factors

Introduction

While the amount of information on many issues related to COVID-19 has increased, the long-term consequences of illness and disability remain largely unclear. In previous studies on COVID-19 infections, besides symptoms such as fever, cough, fatigue, and shortness of breath in the acute phase of the disease[1,2] long-lasting functional and symptomatic abnormalities have also been shown[3]. It is predicted that survivors of COVID-19 may have to deal with physical or psychological problems later. However, the real extent of persistent mood changes and ongoing symptoms in the post-COVID-19 period and whether there are determinants that cause these are still a matter of curiosity. Therefore, studies are needed to identify long-term persistent changes and the prevalence of symptoms, along with contributing factors.

The results of recent studies with small samples have shown that patients with COVID-19 may experience persistent symptoms, particularly fatigue and shortness of breath[4-8]. However, long-term outcomes are mostly based on retrospective data analyses, and symptom severity has not been determined in a broad population of patients. Furthermore, as most cohorts have consisted only of hospitalized patients, their results are insufficient to demonstrate the actual long-term global burden spectrum of the disease. As a matter of fact, when it is aimed to determine the factors that predict permanent symptoms and mood changes in the long term, there is a clear need for studies evaluating patients with both mild and severe forms of the disease. We conducted this study to assess long-lasting symptoms, including fatigue and mood changes, over 3 months and further investigate associated risk factors if any in a cohort that included both mild and severe disease cases.

Materials and Methods

Patients

This single-center prospective cohort study was conducted between 30 July 2021 and 30 September 2021 at a tertiary-care hospital. A total of 132 COVID-19 patients who were treated with or without hospitalization and presented to a follow-up visit at 13±1 weeks after diagnosis were included. SARS-CoV-2 infection was confirmed by positive real-time

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reverse transcriptase-polymerase-chain reaction (RT-PCR) results of nasal and pharyngeal swab samples along with the detection of lung infiltrates on lung CT or chest X-ray in clinically suspected patients. The PCR, clinical, laboratory, and epidemiological data of the cases diagnosed with COVID-19 were recorded as values measured at time 2. Inquiry results and symptoms including FACIT scores 4-6 weeks before diagnosis were recorded as time 1 measurements and taken as baseline values. In addition to patient reports, epidemiological and laboratory data from medical records, patient charts, and databases were used. Accurate information regarding clinical and laboratory parameters was stored in the electronic files of each patient included in the analyses. Along with the recording of the current laboratory and radiological findings of the patients who were seen at their 13±1-week follow-up visit and survived, those who agreed to participate in the study and gave their consent, who had clinical examinations, social changes, symptoms, and comorbidities filled out data collection forms created for the study. We excluded patients whose time between initial presentation and follow-up examination was shorter than 12 weeks or longer than 14 weeks.

Clinical assessment and data collection instruments

All patients had been evaluated and treated by pulmonologists. Patient data, including clinical and demographic data of the patients at diagnosis or at their follow-up visits, were obtained and recorded by the researchers. Comorbidities were recorded based on the self-reports of the patient, and the Charlson Comorbidity Index (CCI) scores of the patients were noted. In CCI assessments, each comorbidity has an associated weight from 1 to 6, based on the adjusted risk of mortality or resource use. For each patient, the standard calculation was conducted[9].

The severity of the disease was defined according to the WHO COVID-19 clinical management guidelines at the time of diagnosis[1]. Oxygen saturation in room air <90%, respiratory rate >30 breaths/min, and severe respiratory distress symptoms (use of accessory muscles, inability to complete a sentence) were defined as severe cases[2], and in the absence of any of these criteria, the cases were considered non-severe. The cases were considered critical based on criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would require mechanical ventilation support (invasive or non-invasive) or vasopressor therapy[10]. The decision of hospitalization or outpatient treatment of the cases was made according to the opinion of the first physician who examined the patient and by considering parameters such as the clinical condition of the patient, radiological imaging results, and the presence of risk factors.

Questionnaires were used to assess persistent symptoms, self-reported functional disability, fatigue, depression, and anxiety. All questionnaires were administered to all patients included in the study at their follow-up visits (13±1 weeks). Each interview lasted approximately 10–15 minutes. A fatigue questionnaire was administered for time 1, time 2, and time 3 measurements at outpatient follow-up visits. In the follow-up visits, functional disability was evaluated objectively using the Instrumental Activities of Daily Living (IADL) Scale. It was defined as a self-reported difficulty or inability to perform any of the following: heavy housework, light housework, shopping, preparing meals, paying bills, or using the phone. The results of IADL are evaluated as 0–8 points: dependent, 9–16 points: semi-dependent, and 17–24 points: independent[11]. Additionally, a validated version of the Beck Depression Inventory (BDI) was used to determine the risk of depression and severity of depressive symptoms, and the Beck Anxiety Inventory (BAI) was used to determine anxiety during the follow-up period. Patients with BDI scores of ≥17 are defined as having a depressive mood[12]. All data obtained at the follow-up visit of the patients (time 3), as well as those obtained at time 1 and time 2, were analyzed to reveal the relationships between relevant risk factors and fatigue.

Statistical Analyses

The analyses were performed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA). The normality of the distributions of the variables was investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Descriptive statistics are presented using mean and standard deviation values for the normally distributed variables and median and interquartile range values for the non-normally distributed and ordinal variables. While investigating the relationships between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance levels were calculated using the Spearman correlation test. Conventional parametric tests were used for comparisons (χ^2 test, Student' t-test). Non-parametric tests were used for comparisons if the variables were not distributed normally, and Fisher's exact test was used to identify the relationships between categorical variables in small samples. Potential relationships between non-normally distributed variables in two independent groups were tested with the Mann-Whitney U test. A p-value smaller than 0.05 was considered to show a statistically significant result.

Results

In total, 132 patients (76 male, 56 female; mean age: 52±12 years) who were previously diagnosed with COVID-19 at a tertiary-care hospital and presented at 13±1 weeks after their diagnosis for follow-ups were included in the study. The distributions of the comorbidities and smoking statuses of the patients were similar between the hospitalized and outpatient categories. The mean CCI score of all patients was 0.60±0.79. The CCI scores of the patients who had been hospitalized were significantly higher than those of the patients who were treated as outpatients (0.7±0.79 vs 0.46±0.78; p=0.026). The most common comorbidities were hypertension (26%, n=34), diabetes (17%, n=23), asthma (24%, n=31), and ischemic heart disease (14%, n=18). The mean BMI of the patients was 29.3±5[24]. It was determined that 40.8% of the patients were obese as defined by a BMI of >30.

The demographic data of the patients are presented in Table 1. The FACIT scores of the patients are presented in Table 2.Eighty (61%) patients were hospitalized for a mean duration of 7.6±8.7 days, and 52 (39%) were treated as outpatients. It was found that 59.8% of the cases were non-severe, while 40.2% were severe. One hundred and three (78%) patients reported at least one symptom at their follow-up visits. The most common effects of the disease at the follow-ups were stated as fatigue (36%, n=48), dyspnea (21%, n=27), and cough (8%, n=10). Fatigue was the most common symptom of both the long-term (36%) and acute (64%) periods of the disease with a follow-up time of 12 weeks.

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Table 1: Demographic characteristics of patients

		n (%)	X±SD (Median)
Sex (n:132)	M	76 (57.6)	
	F	56 (42.4)	
Age			52.3±11.8 (52)
BMI (n:130)			29.3±5.24 (29)
Education		Literate with no formal degree	8 (6.1)
		Primary school	70 (53)
		Middle school	19 (14.4)
		High school	19 (14.4)
		University	16 (12.1)

Table 2: FACIT scores of patients

	X±SD (Median)
Time 1 FACIT Score	4.71±7.04 (1)
Time 2 FACIT Score	41.08±12.61 (46)
Time 3 FACIT Score	13.36±12.37 (10.5)

Table 3: Distribution of symptoms by sex

			F n (%)	M n (%)	p
Fatigue	Time 2	No	21 (37.5)	33 (43.4)	
		Yes	35 (62.5)	43 (56.6)	0.494
	Time 3	No	30 (53.6)	54 (71.1)	0.039
		Yes	26 (46.4)	22 (28.9)	
Dyspnea	Time 2	No	30 (53.6)	32 (42.1)	0.192
		Yes	26 (46.4)	44 (57.9)	
	Time 3	No	37 (66.1)	68 (89.5)	0.001
		Yes	19 (33.9)	8 (10.5)	
Taste and smell impairment	Time 2	No	33 (58.9)	63 (82.9)	0.002
		Yes	23 (41.1)	13 (17.1)	
	Time 3	No	55 (98.2)	73 (96.1)	0.637
		Yes	1 (1.8)	3 (3.9)	

At the follow-up visits of the patients, both dyspnea and fatigue were more prominent in women than in men (34% vs. 11%, p=0.001 and 46% vs 29%, respectively; p=0.03). The distributions of the symptoms of the patients and their comparisons are shown in Table 3.

Long-term symptoms, including fatigue, were not associated with hospitalization status. The hospitalized patients tended to have an increased risk of fatigue as a long-term symptom compared to the non-hospitalized patients (41% vs. 29%, respectively), but this difference was not statistically significant (p=0.10). The post-COVID-19 FACIT scores

Table 4: Correlations of post-COVID-19 FACIT score with post-COVID-19 BDI, BAI, and IADL scores in hospitalized and non-hospitalized patients

			Post-COVID-19 FACIT Score	BDI Score	BAI Score	IADL Score
Post-COVID-19 FACIT Score	Hospitalized	Correlation Coefficient	1	0.691	0.512	-0.347
		Sig. (2-tailed)	.	<0.001	<0.001	0.002
		N	80	80	80	80
	Non-hospitalized	Correlation Coefficient	1	0.536	0.536	-0.21
		Sig. (2-tailed)	.	<0.001	<0.001	0.134
		N	52	52	52	52

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of the patients at 12 weeks were positively associated with their depression and anxiety values (R: 0.55, p=0.0001 and R: 0.42, p=0.0001, while), while these scores were negatively associated with their IADL scores (R:-0.25, p=0.004). Fatigue was not associated with any of the laboratory or clinical characteristics of the patients such as age, CCI scores, length of stay, BMI, oxygen saturation, and disease severity. Additionally, there was no significant correlation between the presence and scores of fatigue for up to 12 weeks and the laboratory results obtained at the follow-up. The long-term FACIT scores of the patients at time 3 were positively correlated with their FACIT scores at time 1 and time 2 (R: 0.367 p=0.0001 and R: 0.328 p=0.0001, consecutively) (Table 4).

There was no significant difference between the hospitalized and non-hospitalized patients in terms of their BDI scores (7±7.22 vs 7.92±7.85) at their post-COVID follow-ups. There was a significant difference between the 2 groups in terms of their BAI scores (6.74±7.42 vs 9.69±8.41) and IADL scores (7.46±1.38 vs 7.98±0.14; p=0.027 and p=0.001, consecutively). At the time of diagnosis, the prevalence of dyspnea among the hospitalized patients was significantly higher compared to the non-hospitalized patients (62.5% vs 38.5%, p=0.007). There was no significant difference between the 2 groups in terms of persistent symptoms at their 12-week follow-ups. The distributions of comorbidities were similar between the hospitalized and non-hospitalized patients.

Discussion

Various clinical conditions such as pulmonary fibrosis, thromboembolic disease, myocarditis, cardiac arrhythmias, and myalgic encephalomyelitis/chronic fatigue syndrome due to the affected organ systems can be seen in the post-COVID period[13,14]. We conducted this study to evaluate the long-term outcomes of COVID-19 infection based on symptom severity to know the impact of post-COVID symptoms and the psychological impairments they cause. The exact mechanisms of long-lasting symptoms or functional/psychological impairments in affected patients are unknown. There is also no consensus yet in terms of predicting who will be the most affected or which effect can be seen predominantly in different subgroup of patients. In this cohort study, we determined that a significant proportion of the patients suffered from long-term symptoms after surviving COVID-19. Fatigue and shortness of breath were the most common persistent symptoms at 12 weeks after COVID-19 infection.

Probability and severity of long-lasting symptoms

The clinical manifestations of acute infection caused by SARS-CoV-2 have been described extensively. Recently, it was reported that symptoms may continue after acute infection, and this condition is named long COVID[4]. Similar to previous results with a follow-up of 2 months or shorter, more than half of the cases in our study were found to experience fatigue at 12 weeks after their SARS-CoV-2 infection[4,15]. Although there is a wide range in terms of follow-up times, the results of previous reports have been similar to those obtained in this study, with the most common symptoms being fatigue and shortness of breath[4,15,16]. Carfi et al.[4], who included only hospitalized patients in their study, reported that 87.4% of patients had at least 1 symptom, particularly fatigue and dyspnea. They also did not indicate the severity of symptoms, especially for fatigue, the most common symptom[4]. Huang et al.[16] stated that those with more severe illness had an increased risk of persistent fatigue, anxiety, and depression. Even in a period of 6 months, the presence of at least 1 symptom was found to be highly prevalent at a rate of 76%, and the most common symptom was fatigue[16]. Although the aforementioned study included results in long-term follow-up, it could not realistically demonstrate the relationship between disease severity and persistent symptom prevalence or severity, as only hospitalized patients were included, which was an important limitation of the study. Indeed, risk factors associated with persistent symptoms, anxiety, and depression were also not analyzed. Our cohort study included both hospitalized and non-hospitalized patients, and we demonstrated the presence of fatigue symptoms in more than one-third of the patients at the end of 12 weeks. Fatigue and shortness of breath were the most common persistent symptoms in this study.

Long-lasting fatigue and associated risk factors

Despite all available information, the long-term health outcomes of COVID-19 and associated risk factors require more research. We showed that being a woman and the severity of illness were risk factors for fatigue reported at the time of diagnosis. Furthermore, we also supported previous reports that being a woman is a risk factor for persistent fatigue at 12 weeks after infection.16 In addition to fatigue persisting in the post-COVID period, dyspnea was also determined at a higher frequency in women than in men. Female sex and having a pre-existing diagnosis of depression/anxiety were over-represented in those with fatigue[15]. In our study, findings similar to previously reported data that female patients have more anxiety, depression, and fatigue symptoms in both the acute and long-term periods up to 3 months were obtained. This suggests that women are more prone to mood changes after such a viral infection. Although several explanations such as hormonal changes, differences in psychological characteristics, or the reporting of mood changes more commonly by women were put forward to be responsible for this sex-specific difference, a clear distinction regarding these parameters has not been reported.

Considering that male patients are at greater risk for severe disease as suggested in previous studies[17], it is a matter of curiosity if they have an increased risk for persistent post-COVID-19 problems. Conversely, at least dyspnea and fatigue as long COVID symptoms were found to be higher in the female patients in this study. Additionally, anosmia as a symptom at presentation to the hospital was more common among the female patients in this study, and this result was similar to previous reports[18].

Although all age groups are known to be affected, the average age varies depending on the characteristics of the group included, the country where a study is conducted, and even the time when the study is conducted. It is not known whether age is a risk factor for long-lasting symptoms and manifestations after COVID-19 infection. In this study, no significant relationships were found between age and other outcomes such as the requirement of hospitalization, the presence of prolonged symptoms, anxiety, and depression, restriction in activities of daily living, or fatigue scores. The absence of a relationship between ongoing fatigue and BMI in the post-COVID-19 period was consistent with limited previously reported data[19].

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As opposed to previously found results in SARS[20] and recently COVID-19 infections in Asian populations, such as those in China[16], we showed that having more severe disease or being hospitalized or not did not seem to be risk factors for the presence of persistent fatigue. In this study, the hospitalized patients tended to have an increased risk of fatigue as a long-term symptom compared to the non-hospitalized patients (41% vs. 29%, respectively), but this difference was not statistically significant. Although factors associated with the length of hospital stay can show a wide range, there is no clear data as to whether they have an impact on post-COVID-19 outcomes. In our study, no significant difference was found in terms of symptom frequency and fatigue in a long-term period, at 3 months, between the hospitalized and non-hospitalized patients. As far as we know, there is no study comparing hospitalized patients and outpatients in terms of long-term post-COVID-19 symptoms. Additionally, considering results of at least 3 months of follow-up, it can be argued that the duration of hospitalization has no significant effect on mood changes, and at least some of the effects of the disease are independent of hospitalization.

In a single-center study including only severe and critically ill patients, it was reported that the disease was characterized by highly persistent symptoms, especially fatigue and shortness of breath (25 % and 35 %, respectively), at follow-up in 3 months[21]. In the same study, it was concluded that neither the initial characteristics of the disease nor radiological and functional characteristics at the end of the follow-up period had a determining role in both of the reported persistent symptoms[20]. Townsend et al. used the Chalder Fatigue Score (CFQ-11) to assess the severity of fatigue in their study[15] which included both hospitalized and non-hospitalized patients. They showed that long-lasting changes were independent of the initial severity of the disease[15]. Although it was a highly valuable result to show that long-lasting changes were independent of the initial severity of the disease, unfortunately, it is not possible to interpret this result as a long-term result because the follow-up period was very short, with a median follow-up of 10 weeks. COVID-19 is clinically very heterogeneous. Hence, both clinical signs and outcomes may vary depending on the severity of the disease. The study conducted by Townsend et al. included both hospitalized and non-hospitalized patients, similar to our cohort, and in their study, it was predicted that more permanent changes may be seen in the follow-up of patients who are more severely affected by the disease[15]. The relationship between disease severity and long-term outcomes is still not clear since there are not enough data. In this cohort study including severe and mild cases, we showed that the initial clinical and radiological findings and laboratory results of the patients did not have a determining effect on persistent symptoms and depressive mood changes at the end of 3 months of follow-up. Moreover, in the comparisons of the mild and severe cases, no significant difference was found in terms of the presence of persistent symptoms and fatigue scores after 3 months of follow-up. The result of our study clearly showed that persistent symptoms and fatigue scores were not associated with disease severity. However, it was observed that the rate of depressive symptoms was significantly higher in the severe cases.

The relationship between chronic fatigue and anxiety is known well[22]. Our study showed a strong relationship between post-COVID-19 fatigue and anxiety, and none of the cases in the cohort had a prior diagnosis of or treatment for anxiety. A strong relationship was identified between the severity of both anxiety and depression and the severity of fatigue. It was shown that viral respiratory diseases can lead to long-term psychopathological outcomes in survivors both in the acute and post-infection periods[23]. It is expected that there would be an increased risk of anxiety and depression associated with severe illness, especially in COVID-19 patients followed up in intensive care units[24]. Although the rates of anxiety and depression are high in COVID-19 patients, the results of studies mostly refer to the acute phase of infection and inpatients, or they include short-term follow-ups with a wide range of variability[25,26]. Additionally, considering that even limited data reflecting longer periods of follow-up mostly come from China, the extent of persistent anxiety and depression after COVID-19 infection should be clearly demonstrated in cohorts that include patients from different geographies and different levels of disease severity. Moreover, the long-term prevalence and consequences of anxiety and depression in COVID-19 patients are not clear. We showed a strong relationship between persistent post-COVID depression and fatigue. In our study, there was no significant difference between the hospitalized and non-hospitalized groups of patients in terms of their depression scores and fatigue prevalence or severity.

In a study involving 20 patients which was planned to determine the relationship between persistent fatigue and autonomic dysfunction, it was noted that fatigue had a strong negative effect on daily functions, and 35% of the patients could not return to work full time[27]. To the best of our knowledge, there is no large-scale study aiming to examine the possible effects of the prevalence and severity of persistent fatigue on the daily lives of patients and their mood changes. In this study, a significant limitation was shown in activities of daily living at the end of 3 months, especially in cases with severe disease, and there was a significant relationship between activities of daily living and fatigue scores. It can be concluded that many survivors may have persistent symptoms which will be harmful to these patients for long time. For this reason, it is important to continue close follow-ups by considering the multifaceted effects of COVID-19 infection.

Conclusion

The results of this study indicated that disease severity was associated with baseline fatigue scores but not with prolonged fatigue scores. We showed that having more severe disease or having been hospitalized or not did not seem to be risk factors for the presence of persistent fatigue and psychological symptoms at 12 weeks of follow-up after infection. Nevertheless, our results indicated that disease severity was associated with an increased risk of having a more depressed and anxious mood at the follow-up[12]. Finally, the risk of having a depressed and anxious mood in at 12-week follow-up was associated with the severity of fatigue in those with severe illness.

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