



Post-COVID-19 fatigue as a major health problem: a cross-sectional study from Missouri, USA

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Abstract

Background Fatigue following acute viral illnesses is a major issue that complicates the clinical course of several epidemic and non-epidemic viral infections. There is a noticeably higher trend of patients with symptoms that persist after initial recovery from acute COVID-19. This study seeks to obtain more data about the prevalence of post-COVID-19 fatigue and the factors associated with higher fatigue frequency among patients who had COVID-19.

Methods A single center cross-sectional study was performed between May 2021 and January 2022 at University Health, Kansas City, Missouri, USA. The Fatigue Assessment Scale (FAS) was utilized to measure post-COVID-19 fatigue. Descriptive and comparative statistics were used to describe clinical and sociodemographic features of patients. Analysis of variance (ANOVA), the chi-square test, and Fisher's exact test were used to examine the statistical association between the FAS score and other clinical and sociodemographic factors.

Results One hundred and fifty-seven patients who had been diagnosed with COVID-19 and diagnosed at University Health were enrolled in our study. Overall, 72% of patients ($n = 113$) were female. The mean \pm standard deviation of the FAS score was 21.2 ± 9.0 . The prevalence of post-COVID-19 fatigue among our studied sample was 43.3%. The findings of this study suggest that female patients have a significantly higher fatigue score compared with male patients ($P < 0.05$).

Conclusions Post-COVID-19 fatigue is a major issue following the initial acute illness with COVID-19, with a prevalence of 43.3%. We recommend implementing standardized measures to screen for post-COVID-19 fatigue, especially among female patients.

Keywords COVID-19 · Fatigue · Post-COVID-19-fatigue

Background

The 2019 novel coronavirus (2019-nCoV) is a new virus for which the initial clinically significant cases started in Wuhan, China. A few months later, the World Health Organization (WHO) declared 2019-nCoV as the causative agent of the new epidemic disease that was later named coronavirus disease 2019 (COVID-19) [1]. This disease affects several body systems, most commonly the upper and lower respiratory tracts [2]. It also manifests with a wide variety

of clinical symptoms, ranging from mild symptoms such as a sore throat, loss of taste and/or smell, to more severe symptoms, including cough, fever, shortness of breath, and multi-organ failure. Other symptoms include fatigue, myalgia, malaise, and diarrhea [3].

Fatigue is defined as a subjective feeling of tiredness, weariness, and lack of energy that exceeds physical exertion, and also negatively impacts a person's ability to perform daily life activities [4]. In addition, fatigue is not alleviated by sleep or rest [5]. Fatigue is thought to be one of the most common symptoms affecting patients experiencing acute and chronic medical illnesses [6]. It not only affects physical health, but also significantly impacts other aspects including cognitive and psychological health [7]. It is also considered a major determinant that negatively impacts health-related quality of life, with more extreme and prolonged effects on this measure than other common symptoms including pain

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and nausea [8]. Fatigue can be classified as a symptom or a disease by itself, such as chronic fatigue syndrome [9].

Acute COVID-19 infection has been associated with fatigue, with a prevalence of about 36% [10, 11]. As the number of COVID-19 cases has increased dramatically since the beginning of the pandemic, there has been a noticeable increasing trend of patients with persistent symptoms past the acute phase. Some of these symptoms include loss of taste/smell, myalgia, chest tightness, non-restorative sleep, and most importantly, intense fatigue [12, 13]. The occurrence of these long-term adverse effects is concerning for a post-viral syndrome [13].

Post-viral fatigue has been reported in several epidemic and non-epidemic viral illnesses. During the 1918 Spanish flu pandemic, intense fatigue was one of the most common long-term symptoms complicating the post-flu period [14]. For the SARS epidemic in 2003 caused by SARS-CoV, Lam et al. [15] found that 40.3% of patients recovering from SARS reported chronic fatigue at the 4-year follow-up assessment. Magnus et al. [16] studied the H1N1 pandemic in 2009 in Norway and surprisingly found that individuals aged less than 30 years were more likely to develop chronic fatigue syndrome after the infection. For non-epidemic viruses, the well-studied cause of post-viral fatigue is Epstein–Barr virus (EBV), the causative agent of infectious mononucleosis, with up to 38% of patients experiencing persistent fatigue 2 months after disease onset [17].

Islam et al. [14] showed how common post-infectious fatigue is among several epidemic viral diseases (such as the Spanish flu and Ebola virus) and non-epidemic viral diseases (e.g., EBV). They clearly described their concern of post-viral fatigue following COVID-19, a view supported by recent surveys and social media postings. Giving these facts and the evolving COVID-19 pandemic, we carried out this study to determine the prevalence and severity of post-COVID-19 viral fatigue and to examine the factors that are associated with greater risk for developing this syndrome.

Methods

Study design

We performed this single-center observational cross-sectional study between May 2021 and January 2022.

Study setting

The study was conducted at University Health, Kansas City, Missouri; this is the primary teaching hospital for University of Missouri Kansas City (UMKC) School of Medicine. We used the medical records at University Health to gather

information about the number of patients who had tested positive for COVID-19 during the study period.

Study population

The number of patients who had tested positive for COVID-19 at University Health between August 1, 2020, and March 1, 2021, was 1029; these patients comprised the study population.

Sample size

We used the Raosoft sample size web-based calculator to estimate our sample size, which was 157. We increased our sample size by 5% to cover patient non-response.

Participants and sampling technique

One hundred and fifty-seven patients were recruited. We set four inclusion criteria for our study:

1. ≥ 18 years old;
2. Patients who had tested positive for COVID-19 by nasopharyngeal polymerase chain reaction (PCR) at University Health between August 1, 2020 and March 1, 2021;
3. At least 4 weeks had passed since the initial diagnosis; and
4. A maximum of 6 months had passed since the initial diagnosis.

We excluded patients with cognitive restrictions that made independent responses to the questionnaire impossible. We also excluded patients with a prior diagnosis of fibromyalgia and/or chronic fatigue syndrome.

Data sources and variables

The questionnaire we implemented to gather data from patients contained two sections, one for sociodemographic information and the other for the validated Fatigue Assessment Scale (FAS). In the first section, we collected the following sociodemographic characteristics: the patient's living arrangement (lives alone or with family), occupation, and smoking status. Data regarding other clinical and sociodemographic factors were obtained by reviewing the patient's electronic medical records. Those were the patient's gender, age, body mass index (BMI), hospitalization status (inpatient versus outpatient), and ethnicity. We categorized ethnicity as White, African American, and others. We also categorized BMI as underweight ($< 18.5 \text{ kg/m}^2$), normal ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25\text{--}29.9 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). In the second section of the questionnaire,

we included the FAS to assess the severity of fatigue in our studied sample. This scale is a standardized instrument for use as a measure of fatigue. It consists of 10 questions, each of which is answered by using a 5-point Likert-type scale ranging from 1 (“never”) to 5 (“always”). The scores on all questions except questions number 4 and 10 were recorded as Q1 = 1, Q2 = 2, Q3 = 3, Q4 = 4, and Q5 = 5. Questions 4 and 10 were reverse scored (Q1 = 5, Q2 = 4, Q3 = 3, Q4 = 2, and Q5 = 1). Michielsen and colleagues [18] developed this scale and analyzed its psychometric properties; they found an internal consistency of 0.9. The FAS total score ranges from 10, indicating the lowest level of fatigue, to 50, denoting the highest. An additional file was supplied to illustrate detailed description of the questionnaire (Additional file 1).

Data collection procedure

After selecting the patients who fit our inclusion criteria, the study team asked to de-identify the patients who met our inclusion criteria. We used the phone numbers recorded in the patients’ charts. The patients were called by one of the research group members; the calls were made Monday through Friday between 08:00 h and 16:00 h. The caller explained the reason for the call and the objectives of our study and offered enrollment in the study. Verbal consent was obtained from all the participants. The patients were asked the questions included in the questionnaire. The participant was considered a non-responder, if they did not respond twice on two different occasions. The calls were not recorded, and participation in the study was voluntary.

Ethical approval

The Institutional Review Board (IRB) of the University of Missouri Kansas City approved our study protocol. We also obtained verbal consent from each patient before including him/her in our study.

Statistical analysis

We entered our data and analyzed it by using R [19]. The data are expressed as the mean (standard deviation) or frequency (percentage). The FAS was the dependent variable. Clinical and sociodemographic factors were the independent variables. We used analysis of variance (ANOVA), the chi-square test, and Fisher’s exact test to examine the statistical association between FAS and other clinical and sociodemographic factors. The significance level was set at $P < 0.05$. We coded the independent variables such as gender, age, BMI, occupation, and ethnicity as dummy variables, with a value of 0, 1, or 2.

Results

Clinical and sociodemographic characteristics

A total of 157 patients who had been diagnosed with COVID-19 and diagnosed at University Health participated in this cross-sectional study. The number of patients who did not answer or refused to participate in our study was 205 patients. Overall, 72% ($n = 113$) of the patients were female and 28% ($n = 44$) were male. The majority of patients (84.1%, $n = 132$) were <60 years old. Most of our patients (61.1%) were obese ($BMI > 30 \text{ kg/m}^2$). Most of the recruited sample (81.5%, $n = 128$) were living with their family, and 59.9% ($n = 94$) of patients in our sample were employed. The vast majority of patients were not smokers (75.8%, $n = 119$). Regarding

Table 1 Socio-demographic and clinical features of the studied sample

| Variable | Number (%) |
|---|------------|
| Age category (years) | |
| ≤ 60 | 132 (84.1) |
| > 60 | 25 (15.9) |
| Gender | |
| Male | 44 (28.0) |
| Female | 113 (72.0) |
| BMI | |
| Underweight | 1 (0.6) |
| Normal range | 31 (19.7) |
| Overweight | 29 (18.5) |
| Obese | 96 (61.1) |
| Living status | |
| Live with family | 128 (81.5) |
| Live alone | 29 (18.5) |
| Occupation | |
| Unemployed | 63 (40.1) |
| Employed | 94 (59.9) |
| Ethnicity | |
| White | 60 (38.2) |
| African American | 76 (48.4) |
| Others | 21 (13.4) |
| Smoking status | |
| Not smoker | 119 (75.8) |
| Smoker | 38 (24.2) |
| Hospitalization status | |
| Outpatient | 118 (75.2) |
| Inpatient | 39 (24.8) |
| Time of interview after diagnosis (months) | |
| < 3 | 32 (20.4) |
| ≥ 3 | 125 (79.6) |

There were 157 total participants

BMI body mass index

ethnicity, 48.4% ($n=76$) were African American, 38.2% ($n=60$) are White, and 13.4% ($n=21$) are of other ethnicities. Most of the patients in our sample (75.2%, $n=118$) did not require hospitalization, while 24.8% ($n=39$) had been admitted to the hospital. We interviewed the majority of our patients (79.6%, $n=125$) 3 months or more from the COVID-19 diagnosis. Further details regarding the clinical and sociodemographic features of our studied sample are shown in Table 1.

Fatigue and health status

In patients who had been diagnosed with COVID-19 and diagnosed at University Health, the mean FAS score was 21.2 with a standard deviation (SD) of 9.0. The prevalence of fatigue in our studied sample was 43.3% ($n=68$ patients); 12.1% ($n=19$) of patients had extreme fatigue, denoted by an FAS score ≥ 35 (see Fig. 1). Table 2 shows the mean and standard deviation for each of the questions of the FAS.

Association between FAS scores and clinical and sociodemographic characteristics

The only variable that displayed a statistically significant association with the FAS score was gender ($P < 0.05$). On the other hand, the patient's age, BMI, living status, occupation, ethnicity, smoking status, hospitalization status, and timing of interview were not significantly associated with the FAS (all P s > 0.05). For more details regarding the association between clinical and sociodemographic variables and the FAS, see Table 3.

Discussion

We have evaluated fatigue among patients who had been diagnosed with COVID-19 and diagnosed at University Health. Although post-COVID-19 fatigue has been studied

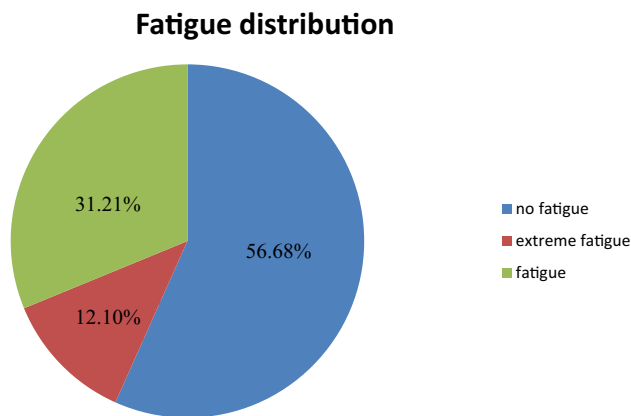


Fig. 1 The distribution of fatigue among the studied sample

Table 2 The mean and SD of the questions included in FAS

| Question number | Question statement | Mean (SD) |
|-----------------|---|-----------|
| Q1 | I am bothered by fatigue | 2.3 (1.4) |
| Q2 | I get tired very quickly | 2.3 (1.4) |
| Q3 | I don't do much during the day | 1.9 (1.2) |
| Q4 | I have enough energy for everyday life | 2.6 (1.5) |
| Q5 | Physically, I feel exhausted | 2.3 (1.5) |
| Q6 | I have problems to start things | 1.7 (1.1) |
| Q7 | I have problems to think clearly | 1.8 (1.1) |
| Q8 | I feel no desire to do anything | 1.8 (1.1) |
| Q9 | Mentally, I feel exhausted | 2.1 (1.3) |
| Q10 | When I am doing something, I can concentrate quite well | 2.5 (1.6) |

SD standard deviation

in other countries such as Saudi Arabia [20], Ireland [21], and India [22], to our knowledge our study is the first to evaluate post-COVID-19 fatigue among the US population. The FAS has been widely used to assess fatigue in different chronic medical conditions such as sarcoidosis [23], systemic lupus erythematosus (SLE) [24], and end-stage renal disease (ESRD) [25]. Our study is the second worldwide and the first in the USA to use this scale to assess post-COVID-19 fatigue; it was previously utilized by El Sayed et al. [20] in Saudi Arabia.

We found that the mean FAS score among patients who had been diagnosed with COVID-19 at our hospital was 21.2 (SD = 9.0). This is lower than the mean FAS score among patients with other chronic medical problems such as ESRD (mean 24.99) [25]. Chronic medical illnesses with significant morbidities can cause severe and more persistent fatigue compared with more acute illnesses such as post-viral fatigue; this might explain the lower percentage of fatigue among our study population [26]. The mean FAS score in our study is lower compared with a similar study of patients who had been diagnosed with COVID-19 in Saudi Arabia (40.81 ± 5.75) [20]. This goes against what has been reported in the literature, namely patients from more developed countries usually have higher fatigue prevalence [27, 28].

The prevalence of post-COVID 19 fatigue in our study was 43.3%. This is higher than the prevalence of post-infectious fatigue reported in other acute viral illness such as EBV (glandular fever), *Coxiella burnetii* (Q fever), or Ross River virus (epidemic polyarthritis) with the prevalence of 12%, as reported by Hickie et al. [29] in their prospective cohort study. The prevalence in this study is also higher than the prevalence of post-viral fatigue of 28% that resulted from Ebola virus infection [30]. Townsend et al. [21] also found a significant burden of fatigue among patients who had been diagnosed with COVID-19 in Ireland, with a 52.3% prevalence of

Table 3 The association between FAS score and socio-demographic and clinical variables among post-COVID-19 patients

| Variable | Number (%) | FAS, number (%) | | | <i>P</i> value |
|---|------------|-----------------|-----------|-----------------|----------------|
| | | No fatigue | Fatigue | Extreme fatigue | |
| Age category (years) | | | | | |
| ≤ 60 | 132 (84.1) | 79 (88.8) | 37 (75.5) | 16 (84.2) | 0.139 |
| > 60 | 25 (15.9) | 10 (11.2) | 12 (24.5) | 3 (15.8) | |
| Gender | | | | | |
| Male | 44 (28.0) | 32 (36.0) | 9 (18.4) | 3 (15.8) | 0.045 |
| Female | 113 (72.0) | 57 (64.0) | 40 (81.6) | 16 (84.2) | |
| BMI | | | | | |
| Underweight | 1 (0.6) | 0 (0.0) | 1 (2.0) | 0 (0.0) | 0.506 |
| Normal range | 31 (19.7) | 14 (15.7) | 12 (24.5) | 5 (26.3) | |
| Overweight | 29 (18.5) | 18 (20.2) | 9 (18.4) | 2 (10.5) | |
| Obese | 96 (61.1) | 57 (64.0) | 27 (55.1) | 12 (63.2) | |
| Living status | | | | | |
| Live with family | 128 (81.5) | 72 (80.9) | 42 (85.7) | 14 (73.7) | 0.483 |
| Live alone | 29 (18.5) | 17 (19.1) | 7 (14.3) | 5 (26.3) | |
| Occupation | | | | | |
| Unemployed | 63 (40.1) | 29 (32.6) | 25 (51.0) | 9 (47.4) | 0.084 |
| Employed | 94 (59.9) | 60 (67.4) | 24 (49.0) | 10 (52.6) | |
| Ethnicity | | | | | |
| White | 60 (38.2) | 34 (38.2) | 21 (42.9) | 5 (26.3) | 0.797 |
| African American | 76 (48.4) | 43 (48.3) | 22 (44.9) | 11 (57.9) | |
| Others | 21 (13.4) | 12 (13.5) | 6 (12.2) | 3 (15.8) | |
| Smoking status | | | | | |
| Not smoker | 119 (75.8) | 71 (79.8) | 36 (73.5) | 12 (63.2) | 0.262 |
| smoker | 38 (24.2) | 18 (20.2) | 13 (26.5) | 7 (36.8) | |
| Hospitalization status | | | | | |
| Outpatient | 118 (75.2) | 68 (76.4) | 37 (75.5) | 13 (68.4) | 0.775 |
| Inpatient | 39 (24.8) | 21 (23.6) | 12 (24.5) | 6 (31.6) | |
| Time of interview after diagnosis (months) | | | | | |
| < 3 | 32 (20.4) | 19 (21.3) | 9 (18.4) | 4 (21.1) | 0.959 |
| ≥ 3 | 125 (79.6) | 70 (78.7) | 40 (81.6) | 15 (78.9) | |

There were 157 total participants

BMI body mass index

post-COVID-19 fatigue, which is similar to what we found. These findings clearly indicate that COVID-19 is one of the major causes of post-viral fatigue compared with other epidemic and non-epidemic viral illness.

Our study demonstrated that female patients have significantly higher FAS scores compared with male patients. Other researchers have reported similar results of higher fatigue frequency in women in other chronic medical illnesses. For example, Mollaoğlu and Üstün [31] found that gender is one of the major determinants of fatigue severity in patients with multiple sclerosis. In patients with cancer, the level of fatigue, anxiety, and depression was also higher in women [32]. In addition, women were significantly more likely to report post-infectious fatigue in other acute viral infections such as West-Nile virus infection [33]. Female gender has also been associated with higher risk for the

development of chronic fatigue syndrome after infectious mononucleosis in adolescents [34]. El Sayed et al. [20] studied post-COVID-19 fatigue and found a significant positive correlation between gender and FAS score ($P < 0.05$). However, they found higher fatigue scores in men (mean FAS in men = 41.5, mean FAS in women = 38.89). Another study on patients who had been diagnosed with COVID-19 in Ireland showed a distinct female preponderance in the development of fatigue after acute COVID-19 infection [21], a finding that is consistent with our study. This can be explained because, in addition to employment, women have other social duties, including taking care of young children; these additional responsibilities might increase their chances of developing post-infection fatigue [35]. The mean age of the female population in this study was 44.4 years. With advancing age, women might have an increased risk of fatigue attributed

to menstrual abnormalities, early menopause, endometriosis, pelvic pain, and hysterectomy [36], which we did not account for in our study.

It is unclear whether viral illnesses can cause or contribute to the development of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [37]. Given the growing number of COVID-19 cases, the emergence of new variants and the persistence of symptoms in a sizable proportion of patients, development of ME/CFS might be a concern in this pandemic. More long-term studies need to be conducted to assess this possible association.

Strengths and limitations

Notwithstanding the relatively limited sample size, this work has many positive points. For example, to our knowledge it is the first study to assess post-COVID 19 fatigue in the US population. Moreover, it is the second study worldwide and the first in the USA to use the FAS to determine the severity of fatigue in patients who had been diagnosed with COVID-19. In addition, we included patients from multiple races given the multiracial nature of our hospital population. On the other hand, there are some limitations we have to mention. First, our study is cross-sectional in nature, so we could not identify a cause-effect relationship and only assessed participants at a single time point. Second, the absence of control groups (i.e., patients with other viral infections such as infectious mononucleosis or influenza) limits the interpretation of the disease burden and its association with fatigue. Furthermore, there are some clinical and social determinants that might affect post-viral fatigue that we did not include in our study, such as educational level, monthly income, and some routine laboratory measures. Moreover, there are concerns for recall bias in the studied sample as participants who agreed to participate in the study were more likely to report fatigue compared with individuals that declined to participate in the study. Lastly, our sample included more women (72%) than men, and this might result in a selection bias.

Conclusion

Following the initial acute illness with COVID-19, post-COVID-19 fatigue seems to be a major health concern, with a prevalence of 43.3% in our study population. This is noticeably higher than post-viral fatigue found in other epidemic and non-epidemic viral infections. Women had significantly higher fatigue in the period following the initial acute illness with COVID-19 compared with men. This study highlights the burden of post-COVID-19 fatigue. Therefore, we recommend implementing standardized

methods in clinical practice to screen for post-COVID-19 fatigue so as to apply early interventions to help patients who experience significant fatigue. We also recommend that health care providers give more attention to female patients following acute COVID-19 illness, because they are at significantly higher risk of developing post-COVID-19 fatigue.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11845-022-03011-z>.

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