Follow-up of COVID-19 Recovered Patients with Mild Disease

Alina Kashif
CMH Lahore Medical College and Institute of Dentistry
Manahil Chaudhry
Hameed Latif Hospital
Tehreem Fayyaz
CMH Lahore Medical College and Institute of Dentistry
Mohammad Abdullah (mohammadabdullah_786@hotmail.com)
CMH Lahore Medical College and Institute of Dentistry
Ayesha Malik
Hameed Latif Hospital
Javairia Manal Akmal Anwer
CMH Lahore Medical College and Institute of Dentistry
Syed Hashim Inam
CMH Lahore Medical College and Institute of Dentistry
Tehreem Fatima
Hameed Latif Hospital
Noreena Iqbal
Milton Keynes Hospital NHS Foundation Trust
Khadija Shoaib
CMH Lahore Medical College and Institute of Dentistry

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Abstract

COVID-19 may manifest as mild, moderate or severe disease with each grade of severity having its own features and post-viral implications. With the rising burden of the pandemic, it is vital to identify not only active disease but any post-recovery complications as well.This study was conducted with the aim of identifying the presence of post-viral symptomatology in patients recovered from mild COVID-19 disease. Presence or absence of eleven post viral symptoms was recorded and we found that eight of the eleven studied symptoms were notably more prevalent amongst the female sample population. Our results validate the presence of prolonged symptoms months after recovery from mild COVID-19 disease, particularly in association with the female gender. Hence, proving the post-COVID syndrome is a recognizable diagnosis in the bigger context of the post-viral fatigue syndrome.

Introduction

The SARS-CoV-2 virus lead to a global health crisis when in November 2019, the first case of COVID-19 was reported in Wuhan, China [1]. COVID-19 primarily targets the respiratory system with variable initial symptoms including fever, sore throat, flu-like symptoms, and diarrhea [2]. There is a chance that some symptoms may linger even after the convalescence phase has subsided. The presence of symptoms after recovery from a viral disease is broadly recognized as post-viral syndrome [3].

To date, various viruses have been associated with this syndrome, including the Coxsackie B Virus, Epstein Bar virus, Influenza virus, *Candida albicans, Borrelia burgdorferi*, Enterovirus, Cytomegalovirus, Human Herpesvirus, Retrovirus, Borna virus, and hepatitis C virus (HCV) [4]. The SARS outbreak in 2003 was due to a virus from the same RNA virus family as SARS-CoV-2, which has an established correlation with the development of several lingering symptoms after recovery from the acute infection [5]. These symptoms include, malaise, myalgias, lack of concentration, and sleep disturbances.

A 131 patient based study in Wuhan revealed that 29% of their patients had persistence of symptoms after a 2-week post-discharge follow up. [6] This is one excerpt that provides evidence of this syndrome being present in COVID-19 patients, hence, we aimed to validate it further. With the second wave of the COVID-19 pandemic rising in on a background of possible prolonged symptoms in previously affected patients from the first wave, the disease burden will only increase. Therefore, it is important to recognize not just active disease but the prevailing effects of prior disease in recovered patients as well.

Materials And Methods

The study participants were patients who accessed the health services at our hospital with mild COVID-19 disease. These patients were either admitted and discharged, or advised home quarantine to begin with. While consecutively including patients in the study, we confined our sample to those who presented with mild COVID-19 disease only, confirmed with a positive reverse transcriptase-polymerase chain reaction

(RT-PCR) for SARS-CoV-2 virus (from a nasopharyngeal or throat swab) between April to June, 2020. Mild disease was classified based on the World Health Organization (WHO) guidelines [7], defined as:

1. Mild clinical symptoms, i.e. fever < 38°C (quelled without treatment)
2. With or without cough (no dyspnea, no gasping, no underlying chronic lung disease)
3. No imaging findings of pneumonia

All patients between the ages of 18 to 65 years, suited to the aforementioned inclusion criteria who consented to participate were enlisted in an electronic patient record, along with their demographic and admission details. The patients were invited for a telephonic follow up 3 months after being discharged from the hospital or three months after onset of symptoms for those patients who were advised home quarantine initially.

Patients with moderate, severe, or critical COVID-19 disease, or those that required intensive care during their admission were excluded from the study. A chest x-ray (CXR) was done for all patients and patients having any infiltrates suggestive of pulmonary involvement by SARS-CoV-2 were excluded. Other features that lead to the exclusion were, patients with missing contact details, those lost to follow up, and those who failed to give consent to participate when contacted for follow up. Furthermore, patients who were diagnosed cases of angina, sleep disorders, psychiatric disorders, chronic fatigue syndromes, and neuromuscular disorders were also excluded, along with those who had cognitive or communication impairment that made the telephonic conversation difficult. All participants were also inquired whether they had contracted any other infections during the three-month window. All patients with concurrent medical illnesses were excluded as well. Lastly, patients who were admitted in an in-patient facility at the time of follow up were also excluded.

A total of 266 patients were contacted, out of these, 26 could not be reached out and only 242 were included in the final sample. Each person was then questioned about the demographic and admission details which were cross-checked with the electronic record to confirm the identity. They were asked an open-ended question regarding their health and feeling of any sort of symptom to identify the general self-reported health status before any formal questioning.

The presence or absence of the following post-viral symptoms was asked and noted: cough, nausea/vomiting, headache, sleep disturbances (such as insomnia and unrefreshing sleep), decreased appetite, chest pain (chest discomfort that did not classify as angina, i.e. did not have the following signs: substernal discomfort of characteristic quality and duration, provoked by exertion or emotional stress and relieved by rest/nitrates), low mood, dizziness, palpitations, myalgias, and fatigability. This list of symptoms was designed after careful review of previous literature on symptoms associated or attributed to post-viral syndrome.

A formal approval from Combined Military Hospital Lahore Ethical Review Board (ERC# 251/2020) was sought prior to initiation of the study and informed consent was sought from all patients. The study was

conducted in lines with the principles laid down in the declaration of Helsinki. Demographic data and comorbidities were recorded. The data was analyzed using SPSSv25. Descriptive statistics were run for continuous data.

Results

In total, two hundred and forty two patients were included in the study, out of which 168 (69.4%) of these were male while 74 (30.6%) were females. Altogether, presence of 11 post viral symptoms was studied. The frequency and percentage of these symptoms is shown in Table 1.

Table 1
– Frequency and percentages of various post-COVID symptoms in descending order of prevalence

Symptom	Frequency	Percentage
Fatigability	101	41.7%
Myalgias	85	35.1%
Decreased appetite	58	24%
Sleep disturbances	51	21.1%
Headache	46	19%
Low mood	44	18.2%
Dizziness	35	14.5%
Palpitation	30	12.4%
Nausea/Vomiting	29	12%
Chest Pain	26	10.7%
Cough	16	6.6%

The sample was stratified into two groups, those without any co-morbidities and those with co-morbidities present, either of diabetes mellitus (DM), hypertension (HTN) and ischemic heart disease (IHD).

Overall, only twenty-nine people reported having one or more comorbidities while the rest 213 had none as shown in Table 2. It was also noted that the group of people with comorbid conditions had a mean age of 50.23 ± 12.04 years as compared to the group having no co-morbidities and average age of 33.65 ± 11.29 years ($p < 0.00001$). Two of the symptoms were significantly more prevalent amongst the group with co-morbidities, namely decreased appetite ($p = 0.023$) and sleep disturbances ($p = 0.004$). For the

remaining symptoms there was no significant difference in frequency of occurrence between these two groups.

Table 2
– Comparison of symptomatology amongst patients with and without co-morbidities

	Co-morbidities (n = 29)		**No Co-morbidities (n = 213)**		**P-Value**
	Frequency	**Percentage**	**Frequency**	**Percentage**	
Fatigability	13	44.8%	88	41.3%	0.647
Myalgias	13	44.8%	72	33.8%	0.223
Palpitation	1	3.4%	29	13.6%	0.119
Dizziness	4	13.8%	31	14.6%	0.913
Low mood	8	27.6%	36	16.9%	0.162
Chest Pain	2	6.9%	24	11.3%	0.476
Decreased appetite	12	41.4%	46	21.6%	**0.0230**
Sleep disturbances	12	41.4%	39	18.3%	**0.00427**
Headache	8	27.6%	38	17.8%	0.210
Nausea/Vomiting	5	17.2%	24	11.3%	0.690
Cough	2	6.9%	14	6.6%	0.948

Analysis and comparison of symptomatology in accordance with gender was carried out as shown in Table 3. It depicts that eight of the eleven studied post-viral symptoms had a significantly greater occurrence amongst females as compared to males. These included myalgias, decreased appetite, headache, low mood, nausea/vomiting, chest pain, sleep disturbances, and fatigability. Other symptoms including palpitations, cough and dizziness had no significant variation with gender.

Table 3
– Mean age and gender differences across the post-COVID symptoms

	Frequency	Age (mean ± SD)	Male	Female	P-Value
Myalgias	85	36.39 ± 13.75	44	41	**< 0.00001**
Decreased appetite	58	36.44 ± 15.53	28	30	**0.000051**
Sleep disturbances	51	37.33 ± 14.32	27	24	**0.00435**
Headache	46	34.83 ± 12.67	23	23	**0.00161**
Low mood	44	34.14 ± 13.18	23	21	**0.00575**
Fatigability	101	35.59 ± 13.79	63	38	**0.039**
Chest Pain	26	33.23 ± 9.25	11	15	**0.00137**
Nausea/Vomiting	29	35.25 ± 13.58	14	15	**0.00889**
Dizziness	35	31.31 ± 11.04	23	12	0.0213
Palpitation	30	33.3 ± 10.77	21	9	1.00
Cough	16	32.32 ± 12.2	12	4	0.609

Discussion

While Halpin et al. [8] referred to them as “post-discharge” symptoms in a COVID-19 follow-up study, Islam et al. broadly described them as “post-viral fatigue” symptoms [9]. We aimed to infer whether these symptoms, which include, malaise, myalgias, lack of concentration, sleep disturbances, and others, were present following infection with COVID-19 disease. Existing literature has described the post-viral fatigue in moderate to severe cases of coronavirus recovered patients, it was unclear whether mild cases exhibited a similar symptomatology. One of the reasons from the rationale of studying mild cases only, was that Demeco et al. [10] reported that in the majority, 81% of patients, COVID confers a mild disease. In addition, Garg et al. [11] suggested in an editorial that a subgroup analysis of only mild COVID-19 patients would provide more insight to the post-viral fatigue syndrome as there is a scarce chance of chronic organ impairment in these cases. Therefore, in this study we aimed to identify residual symptoms in patients who recovered from mild COVID-19 disease due to infection by the SARS-CoV-2 virus.

Though a number of studies are still underway, and no consensus has been reached regarding the cut-off for how long the post-viral symptoms persist, following are some notable reported narratives. A study in Wuhan of 131 patients found that 29% of their patients had persistence of symptoms at a two week follow up [6]. Carfi et al. [12] reported that, 87.4% recovered patients had persistence of at least one symptom, particularly fatigue and dyspnea at an average of 48 days post-discharge. In a survey led by

the center for disease control and prevention (CDC) COVID-19 response team, amongst symptomatic adults with mild disease patients, 35% of the participants had not returned to their usual baseline health at 14–21 days after testing positive, with 47% amongst these being ≥ 50-years old [13].

Halpin et al. [8] observed that fatigue was the most commonly occurring symptom during follow-up for both ward (60.3%) and ICU (72%) patients, followed by respiratory symptoms (shortness of breath), while in our study, respiratory sequelae (cough and chest pain) were the least prevalent. It should be taken into consideration that moderate to severe cases of coronavirus result in diffuse lung injury, pulmonary infiltrates along with respiratory distress. Furthermore, the patients in an ICU setting may require mechanical ventilation secondary to acute respiratory distress syndrome (ARDS) and pulmonary fibrosis. It can be inferred that persistence of respiratory symptoms seen in such cases may stem from long-term lung injury associated with more severe forms of the disease and hence, were not observed in our cohort.

A notable result from our study was the occurrence of sleep disturbances in 18.3% of healthy adults without any co-morbid conditions, which formed majority of the sample population (88%), and in 41.4% of patients with existing co-morbidities, which was a statically significant finding. This renders that a strong correlation exists between disordered sleep and the presence of co-morbidities. Altered sleep patterns have previously been reported by Moldofsky et al. [5] who documented the presence of non-restorative, unrefreshing sleep for as long as 19.5 months in patients suffering from the chronic post-SARS syndrome (2003). Another study by Xiong et al. reported 17.7% of their survivor cohort had sleep disorders after the onset of the disease [15]. It shows that not only can disturbed sleep occur in all age groups, but for prolonged time periods as well. Altered sleep can be owing to isolation during lockdown, social distancing from family and friends and phobias associated with the pandemic.

There was an evident association of majority of the symptoms, specifically, decreased appetite, chest pain, headache, low mood, sleep disturbances, fatigability, myalgias, and nausea/vomiting with female gender. Similarly, Xiong et al. [15] related physical decline/fatigue, post-activity polypnea and alopecia as being significantly more common in female survivors. Thus, an association of post-COVID sequelae with gender exists and demands further research.

We acknowledge some shortcomings in our study. Ours was a single-center study with a small sample size and the findings weren't compared with a control group. Moreover, there always exists some element of recall bias with follow-up studies. The post-COVID syndrome is a fairly new dilemma seen in COVID survivors and we still know relatively less about the long-term effects of the disease as we have only months of experience to draw on. Additionally, in more severe forms of the disease, the occurrence of the cytokine storm has proven to be a predictor of chronic fatigue syndrome (CFS) like symptoms in COVID-19 survivors, whereas, for less severe forms of the disease, there is still a need to study the pathogenesis leading to the occurrence of the post-COVID syndrome which cannot be explained entirely by the cytokine storm. Lastly, it is important to include various ethnicities and socio-demographically diverse groups in study samples to study the association of the post-COVID syndrome with the ethnicity.

Conclusion

We reported various post viral sequelae, the most common being fatigue, in mild-COVID-19 recovered patients three months after being discharged. Post-COVID syndrome warrants recognition as a medical diagnosis and henceforth, measures like rehabilitation, awareness groups, and most importantly, symptomatic treatment to be offered to patients even after culmination of the disease, especially in those with “mild” disease as they can often be ignored in the realm of the pandemic.

Declarations

Conflict of interest

The authors have no conflict of interest to declare

Author Contribution Statement

AK – project lead

MA – writing the manuscript

TF – writing the manuscript

MA – writing the manuscript

AM – data collection and manuscript editing

JMAA – data collection

SHAI – data collection

TF – data collection

NI – proof reading and formatting the manuscript

KS – data collection

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