

Research Article

Persistent Symptoms at the End of 3 Months after Acute COVID-19 Infection among Adult Patients Admitted to a Tertiary Care Centre: A Descriptive Longitudinal Study

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A B S T R A C T

Background: COVID-19 has affected all corners of the world. Multiple symptoms reported during the hospital stay may persist after the patient discharged from the hospital. **Objectives:** 1) To study the persistence of symptoms at the end of 3 months after acute COVID-19 infection among adult patients admitted to a tertiary care centre. 2) To review their symptoms during the acute COVID-19 infection. 3) To study the association between various factors and the persistence of symptoms of acute COVID-19 infection.

Material & Method: This was a descriptive longitudinal study conducted in November 2021. The sample included 200 laboratory-confirmed COVID-19 cases discharged from the tertiary care hospital of Pune City after obtaining written informed consent. Epidemiological information was obtained by telephonic interview with predesigned and pretested proforma covering socio-demographic data, related factors and information about the onset and duration of symptoms after the patient was discharged from the hospital.

Results: The study involved 200 recovered COVID-19 patients (115 males, 85 females) with a mean age of 46.42 ± 16.22 years. Notably, 90% of males had some form of addiction, compared to 10% of females, revealing a significant gender disparity (p value < 0.0001). Fatigue (75.50%), cough (73%), and fever > 38.0 °C (69.50%) were prevalent persistent symptoms. A statistically significant association of persistence of symptoms was found with age and COVID-19 vaccination status.

Conclusion: Our study provides crucial insights into long-term COVID-19 symptoms, advocating targeted interventions considering demographic factors. This comprehensive approach guides effective management of persistent symptoms post-COVID-19.

Keywords: Acute COVID-19, Persistent Symptoms, Longitudinal Study, Post-COVID-19

Introduction

COVID-19 has affected all corners of the world. India stands at the 2nd position after the United States which had 45,035,254 cases and 533568 deaths.^{1,2} Multiple symptoms have been reported during the hospital stay like fever, cough, fatigue, dyspnea, headache, diarrhoea, nausea, vomiting etc., and these may persist after the patient has been discharged from the hospital.³⁻⁵ The post-COVID syndrome, also called the Long COVID syndrome, is characterised by persistent physical, medical and cognitive sequelae following COVID-19 infection, including persistent immunosuppression and pulmonary, cardiac and vascular fibrosis.⁶ Pathologic fibrosis of the organs and vasculature increases mortality and severely worsens quality of life.⁶

There are varying definitions of Post-Acute Sequelae of COVID (PASC) as follows:

- **Acute COVID-19:** Signs and symptoms of COVID-19 lasting up to 4 weeks after the patient tested positive for RT PCR or rapid antigen test.⁷
- **Ongoing symptomatic COVID-19:** COVID-19 signs and symptoms from 4 to 12 weeks.⁷
- **Post-COVID-19 syndrome:** Signs and symptoms that develop during or after an infection consistent with COVID-19, persist for more than 12 weeks and cannot be explained by alternative diagnosis.^{7,8}

As of June 1, 2021, India had crossed 28 million confirmed cases and 3,31,909 deaths,¹ of which 57,46,892 cases and 95,344 deaths were in the state of Maharashtra alone.⁹ The mortality rate of the disease in Maharashtra was around 1.66% which was more than the national average.⁹ On March 9, 2020, the first confirmed case of novel coronavirus in Maharashtra was reported in Pune. As of 1st June 2021, the total cases in Pune were 4,69,747.¹⁰

Post-COVID symptoms persist in 35% of outpatients treated with COVID-19 and in 87% of hospitalised patients, depending on the study population.^{4,11} There has been an increasing concern about the long-term effects of the post-COVID syndrome as more and more patients are discharged from the hospital, placing an increasing burden on healthcare systems, patients' families, and society, in general, to care for these medically devastated COVID-19 survivors.⁶ Hence, a study was planned to explore possible manifestations of persistent post-COVID-19 syndrome and will also help to guide and counsel post-COVID-19 individuals for appropriate treatment.

Study Objectives

- To study the persistent symptoms at the end of 3 months after acute COVID-19 infection among adult patients admitted to a tertiary care centre

- To review and study their symptoms during the acute COVID-19 infection
- To study the association between various factors and the persistence of symptoms of acute COVID-19 infection

Materials and Methods

A hospital-based descriptive longitudinal study was conducted in a tertiary care hospital in Pune City in November 2021 after obtaining Ethics Committee clearance. The data of laboratory-confirmed cases of COVID-19 patients with persistent complaints, admitted and discharged in November 2021 from a tertiary care hospital in Pune City were enrolled in the study. All laboratory-confirmed COVID-19 cases from areas outside Pune city were excluded. Patients who were not willing to participate, patients below 18 years of age and those with incomplete information were also excluded.

Considering the prevalence of post-COVID symptoms to be 35% in outpatients treated with COVID-19 and 87% in hospitalised patients.¹¹ By taking 87% value for hospitalised patients, the minimum sample size to be covered was calculated to be 181 with 95% confidence level, 5% absolute precision and 80% power and rounded off to 200 with a non-response rate of 10%. The sampling method was simple random sampling. The list of admitted laboratory-confirmed cases for COVID-19 above 18 years of age had been obtained from a tertiary care hospital in Pune. Besides some general questions about socio-demographic profile, pre-existing comorbidities, self-reported health status (good/ moderate/ poor) before the onset of symptoms and follow-up, date of onset of symptoms, date of COVID-19 diagnosis and clinical health status at the time of isolation (mild/ moderate/ severe), healthcare utilisation after the infection (e.g. general practitioner/ physiotherapist/ medical specialist/ psychologist/ dietician/ other than this) and there was a follow up of symptoms i.e. Increased body temperature (37.0-37.9 °C). Fever (body temperature \geq 38.0 °C), cough, sputum production, runny nose, sneezing, breathlessness, sore throat, fatigue, muscle pain, joint pain, loss of smell, loss of taste, headache, vertigo, diarrhoea, nausea, vomiting, red spots on toes/ feet, pain/ burning feeling in the lungs, ear pain, chest tightness, pain between shoulder blades, heart palpitations, increased resting heart rate, eye problems, sudden loss of body weight, gain in body weight, burning feeling in the trachea, hot flushes, chest pain, brain fog, anxiety, depression, significant hair loss, loss of appetite and others. A history of vaccination was taken.

Epidemiological information was obtained by telephonic interview with predesigned and pretested proforma. The

interviews of the patients were taken six times at the time of admission and further on November 30, 2021, December 15, 2021, December 30, 2021, January 15, 2022, and January 30, 2022 by the trained staff of the Department of Community Medicine after obtaining their written informed consent. The first physical visit was to gather socio-demographic information such as name, age, sex, religion, occupational history, family history, past history, onset and symptoms at onset and the remaining five calls were for information about the duration of symptoms and persistent symptoms after the patient was discharged from the hospital.

Ethical Considerations

Approval for this study has been granted by the Institutional Ethics Committee (IEC). BJGMC/IEC/Pharmac/ND-Dept 0721262-262/15/09/2021. Participants in the study were informed about the study's objectives and their right to refuse participation at the time of admission to the hospital. Respondents' information was kept confidential and was only used for research purposes.

Data Analysis

Data entry was done in Microsoft Excel. The data was tabulated and analysed using SPSS version 23. The chi-square test was used to find the association.

Results

Demographic data and clinical characteristics of involved study participants are expressed in Table 1. The study involved 200 recovered COVID-19 cases, 115 of whom were males and 85 females. The age of involved subjects expressed as mean \pm SD was 46.42 ± 16.22 years, ranging from 18 to 81 years old. The mean \pm SD of weight was 66.63 ± 12.33 kgs, the mean \pm SD of height was 155.99 ± 10.14 cm and the mean \pm SD of body mass index was 27.38 ± 4.58 kg/m².

Proportion of addiction and substance use among male and female subjects. Regarding gender differences in addiction i.e., a significantly higher percentage (90%) of males have some form of addiction compared to female subjects (10%). This suggests a substantial gender disparity in addiction rates within the study subjects. Of these, 65.38% have an addiction to smokeless tobacco. Males have a higher rate of addiction to smokeless tobacco (9%) compared to females (1%). Regarding addiction to tobacco smoking among smokers, 100% of male subjects have an addiction to smoking, while there is no history of smoking among female subjects. Of the total, 34.61% gave a history of alcohol addiction. Males have a notably higher rate of alcohol addiction (94%) compared to females (6%). Overall substance use among study subjects shows that smokeless

tobacco addiction and alcohol addiction are relatively prevalent in the sample, affecting a significant portion of the subjects. Addiction to tobacco smoking is less common in the overall sample but appears to be exclusively in males (p value <0.0001).

Regarding other comorbidities, 70% had no known history of comorbidities; among others, 48.33% had diabetes mellitus and 58.33% had hypertension. Various types of comorbidities among study participants are shown in Figure 1.

The majority of the study participants were hospitalised for COVID-19 treatment for 2 weeks (Table 2). Persistent symptoms of acute COVID-19 infection at the end of 3 months are shown in Table 3. This shows that 74.37%, i.e. 148 study participants, had recovered from persistent symptoms of acute COVID-19 infection within 3 months and 25.63%, i.e. 51 study participants, had not recovered from persistent symptoms of acute COVID-19 infection within 3 months and had persistent symptoms beyond 3 months. The clinical status of the study participants at the time of isolation showed 54% mild, 32% moderate, and 15% severe presentation. Duration-based distribution of study participants having Persistent symptoms of acute COVID-19 infection is shown in Figure 2. The distribution of various persistent symptoms of acute COVID-19 infection is shown in Figure 3. More than 50% of subjects suffered from fatigue (75.50%), cough (73%), fever > 38.0 °C (69.50%), joint pain (62.50%), increased temperature 37.0 to 37.9 °C (61.50%), breathlessness (60.50%), and muscle pain (59.50%).

The association between various factors among study participants at the time of isolation and the persistence of symptoms are shown in Table 4. A statistically significant association was found between the age of the study participants and the persistent symptoms of COVID-19. The majority of the study participants having persistent symptoms of COVID-19 i.e. 25 (32.47%) and 16 (34.04%) were in the age group of 18 to 40 and \geq 61 years in the study, respectively. Study participants in the age group of 41 to 60 years, i.e. middle age group population, were found to be more protected as compared to the young and geriatric age group population. Also, a statistically significant association was found between COVID-19 vaccination status among study participants and persistent symptoms of COVID-19. The majority of the study participants who had not taken the COVID-19 vaccine, i.e. 32 (31.68%), showed persistent symptoms, followed by those who had taken the first dose of COVID-19 vaccine, i.e. 12 (26.67%), and those who had taken two doses of COVID-19 vaccine, i.e. 7 (13.21%) had protective effects against persistent symptoms of COVID-19.

Table 1. Demographic and Clinical Characteristics of the Study Participants N = 200

Variables	Frequency	Percentage
Age in years		
18–40	78	39.0
41–60	75	37.5
≥ 61	47	23.5
Gender		
Male	115	57.5
Female	85	42.5
BMI		
Undernutrition (≤ 18.4)	7	3.5
Normal (18.5–24.9)	50	25.0
Overweight (25–29.9)	84	42.0
Obese (≥ 30)	59	29.5
History of addiction		
Present	52	26.0
Absent	148	74.0
History of co-morbidities		
Present	60	30.0
Absent	140	70.0

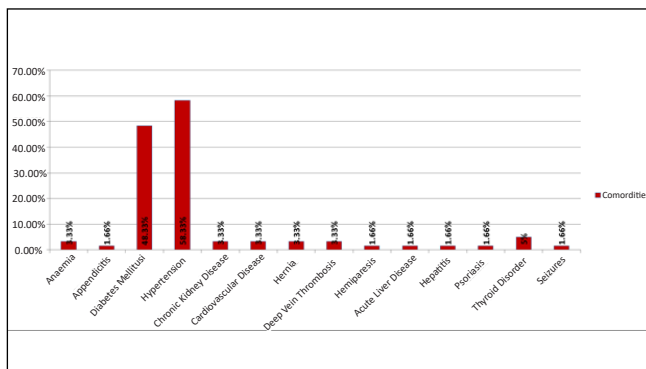


Figure 1. Various Types of Comorbidities among Study Participants

Table 2. Duration of Hospital Stay of the Study Participants

Duration of Hospital Stay of the Study Participants (in Days)	Frequency	Percentage
1–7 (Week 1)	78	39.0
8–14 (Week 2)	101	50.5
15–21 (Week 3)	13	6.5

22–28 (Week 4)	3	1.5
29–36 (Week 5)	5	2.5
Total	200	100.0

Table 3. Persistent Symptoms of Acute COVID-19 Infection at the End of 3 Months

Persistent Symptoms of Acute COVID-19 Infection at the End of 3 Months	Frequency	Percentage
Present	148	74.37
Absent	51	25.63
Total	199	100.00

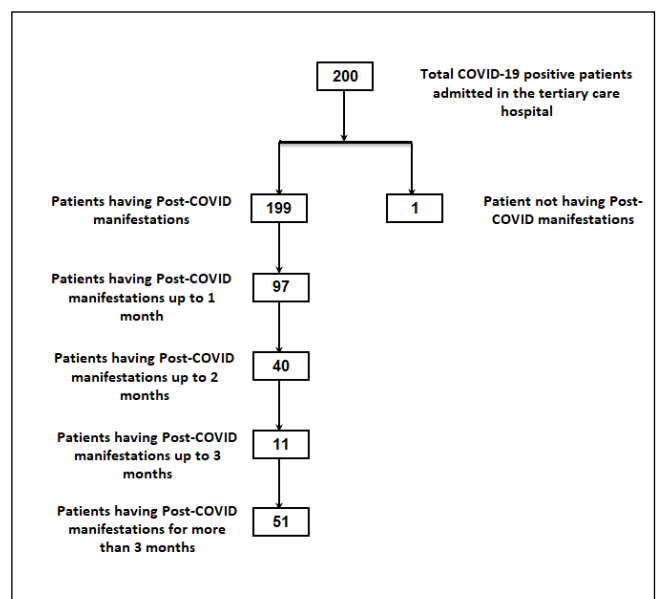


Figure 2. Duration-Based Distribution of Study Participants having Persistent Symptoms of Acute COVID-19 Infection

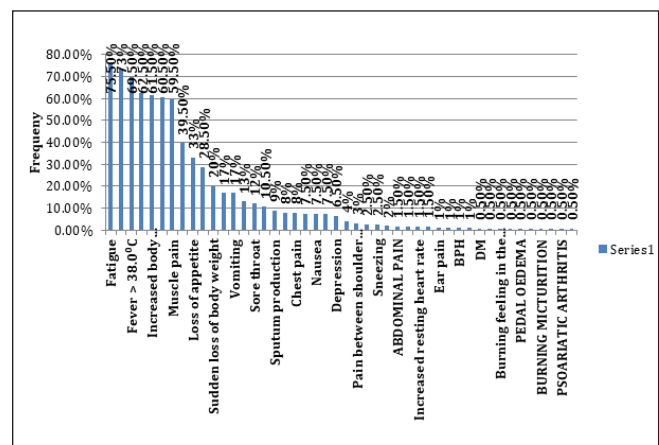


Figure 3. Persistent Symptoms of Acute COVID-19 Infection

Table 4. Association between Various Factors among Study Participants at the Time of Isolation and Persistence of Symptoms

Various Factors	Persistence of Symptoms		N = 199	x ²	p Value
	Present N = 51, 25.63%	Absent N = 148, 74.37%			
Clinical status of the study participants at the time of isolation					
Mild	27 (25.47)	79 (74.53)	106	0.07	0.9640
Moderate	16 (25.00)	48 (75.00)	64		
Severe	8 (27.59)	21 (72.41)	29		
History of addiction of comorbidities					
Present	16 (26.67)	44 (73.33)	60	0.04	0.8200
Absent	35 (25.18)	104 (74.82)	139		
Age in years					
18–40	25 (32.47)	52 (67.53)	77	9.58	0.0083
41–60	10 (13.33)	65 (86.67)	75		
≥ 61	16 (34.04)	31 (65.96)	47		
Gender					
Male	31 (27.19)	83 (72.81)	114	0.34	0.5500
Female	20 (23.53)	65 (76.47)	85		
BMI					
Normal (17.8–24.9)	12 (21.05)	45 (78.95)	57	2.75	0.2500
Overweight (25.0–29.9)	19 (23.17)	63 (76.83)	82		
Obese (≥ 30.0)	20 (33.33)	40 (66.67)	60		
Addiction					
Present	14 (26.92)	38 (73.08)	52	0.06	0.8000
Absent	37 (25.17)	110 (74.83)	147		
Duration of stay in hospital					
1–7 (Week 1)	19 (24.36)	59 (75.64)	78	2.08	0.3500
8–14 (Week 2)	29 (29.00)	71 (71.00)	100		
15–36 (Week ≥ 3)	3 (14.29)	18 (85.71)	21		
COVID-19 Vaccination Status					
Vaccination not taken	32 (31.68)	69 (68.32)	101	6.258	0.0400
1st dose	12 (26.67)	33 (73.33)	45		
2nd dose	7 (13.21)	46 (86.79)	53		

Discussion

This is a descriptive longitudinal study with 200 participants. Important findings are discussed ahead.

In this study, 200 laboratory-confirmed cases of COVID-19 patients were followed up from the admission date in the tertiary care centre. To study the persistent symptoms at the end of 3 months after acute COVID-19 infection, to study their symptoms of acute COVID-19 infection and to study the association between various factors and the persistence of symptoms of acute COVID-19 infection among adult patients admitted to a tertiary care centre.

In this study, 99.50% of patients reported experiencing at least one symptom during the follow-up period. Our study

further solidifies the absence of an association between the severity of COVID-19 during hospitalisation and the level of symptom burden observed during follow-up.

From this study, self-reported fatigue emerged as the most prevalent complaint among a substantial cohort of COVID-19 patients. Similar findings were reported by Sudre et al.¹² in which data collected from the COVID Symptom Study App revealed self-reported fatigue as the most prevalent complaint among a significant population of COVID-19 patients. If these symptoms persist at the four-month mark, they would satisfy the diagnostic criteria for Chronic Fatigue Syndrome (CFS) as outlined by the National Institute for Health and Care Excellence (NICE). A diagnosis of CFS is considered when patients present with symptoms

such as post-exertional fatigue, cognitive impairments, sleep disturbances, and chronic pain.¹³ This symptom complex bears a striking resemblance to those observed in Long-COVID, as noted by their research and other studies. The predominance of females in this presentation aligns with established findings in the CFS literature.¹⁴ Additionally, there is a documented association between obesity and increased symptom severity.¹⁵ However, in this study, neither of these demographic factors exhibited an association with increased symptom severity. CFS services in the UK offer a personalised approach to patient management. A comprehensive array of services is offered, encompassing symptom management, psychological interventions, vocational assistance, and educational resources regarding their condition.¹³ Incorporating these principles into long-COVID service provision may be deemed appropriate to ensure the effective management of our patients.

In this study, gender disparities in addiction rates have been observed, with higher prevalence among males, particularly in the context of smokeless tobacco and alcohol addiction. This underscores the necessity for gender-specific interventions and customised healthcare strategies. The prevalence of comorbid conditions, such as diabetes mellitus and hypertension, is also considerable. This bears potential implications for the persistence of symptoms and the overall process of recovery.

In our study, the duration of hospitalisation predominantly spanned two weeks, with the majority of patients being admitted for a period of 14 days and the study conducted by Chen et al. documented an extended length of hospital stay, averaging 18 days,¹⁵ and some other studies in Wuhan,^{16,17} where the mean length of hospital stay (LOS) for COVID-19 patients was approximately 12 days. These variances could be attributed to the non-representative nature of the study populations, which may not fully encompass all cases diagnosed and treated within tertiary care centres. Numerous patients may have been transferred to hospitals later in the course of their illness during the initial outbreak. Furthermore, inadequate medical resources may have played a role in the premature discharge of certain patients to accommodate incoming cases.

Statistically significant associations were identified between age and COVID-19 vaccination status with the persistence of symptoms. Young adults aged 18 to 40 years and the geriatric population aged 61 years and older exhibited a higher susceptibility to persistent symptoms. A similar finding was reported in a study by Fumagalli et al.¹⁸ Advanced age and male gender have been associated with a more aggressive COVID-19 acute phenotype and, thereby suggesting that older males may experience a prolonged persistence of symptoms over the long term.^{19,20}

While exercising caution in evaluating individuals under the age of 65, reports indicate a significant association between pre-frailty and increased morbidity, such as ischemic heart disease and COPD, as well as mortality across all age groups. These findings suggest that identifying and addressing pre-frailty in both older and middle-aged patients could serve as an effective approach to enhancing healthcare and clinical results.²¹ Furthermore, individuals who had not been vaccinated against COVID-19 demonstrated a greater prevalence of persistent symptoms. This emphasises the potential protective role of vaccination in mitigating prolonged symptomatology, thereby endorsing continued global vaccination initiatives. In our study, more than 50% of subjects suffered from fatigue (75.50%), cough (73.00%), fever > 38.0 °C (69.50%), joint pain (62.50%), increased temperature 37.0 to 37.9 °C (61.50%), breathlessness (60.50%), muscle pain (59.50%), while in the study conducted by Tenforde et al., involving 274 symptomatic outpatients, the median number of symptoms reported was seven out of 17, with fatigue (71%), cough (61%), and headache (61%) being the most frequently documented. Among participants who reported experiencing fever and chills on the day of testing, these symptoms resolved in 97% and 96% of individuals, respectively. The symptoms with the lowest resolution rates were cough, which persisted in 43% (71 out of 166) of cases, and fatigue, which persisted in 35% (68 out of 192) of cases. Among the 90 individuals who reported shortness of breath at the time of testing, this symptom remained unresolved in 26 (29%) cases. They additionally documented the lengthiest durations for loss of smell, with a median of 8 days (interquartile range [IQR] = 5–10.5 days), and loss of taste, with a median of 8 days (IQR = 4–10 days). Among participants who indicated a return to their typical state of health, 34% (59 out of 175) continued to report one or more of the 17 queried COVID-related symptoms at the time of the interview.¹¹

Limitations of the Study

The study is conducted among the admitted patients in just one hospital due to easier access and feasibility. Had this been conducted multi-centrally, the observations might have increased and much more varied.

The telephonic interviews conducted in the study might be limiting the scope. This too was due to the apprehension of having medical personnel from hospitals entering households when the pandemic was ongoing. A well-equipped medical team would have led us to more specific and systematic observations.

Conclusion

This indicates a high persistence of symptoms in the studied population even after the acute phase.

Fatigue was identified as the most common complaint among a large group of COVID-19 patients. More than 50% of subjects suffered from various symptoms such as cough, fever, joint pain, increased temperature, breathlessness, and muscle pain being the most prevalent. The study suggests that if these symptoms persist at four months, they may meet diagnostic criteria for Chronic Fatigue Syndrome (CFS). There is a need for tailored management approaches, including psychological treatments and support services. The study reinforces that there is no significant association between the severity of COVID-19 during hospitalisation and the burden of symptoms at the three-month follow-up. This suggests that the initial infection's severity may not predict the symptoms' persistence.

The comorbid conditions such as diabetes mellitus and hypertension being the most common.

Young adults (18-40 years) and the geriatric population (≥ 61 years) were more prone to persistent symptoms. Participants who had not received the COVID-19 vaccine exhibited a higher prevalence of persistent symptoms, emphasising the potential protective effect of vaccination.

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Conflict of Interest: None

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