

Prevalence and determinants of post-COVID-19 syndrome among patients 6 months post-discharge from a teaching hospital in South India

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) infection has affected millions of people worldwide in the last 4 years. Among those infected, the long-term COVID-19 syndrome, in which symptoms of COVID-19 persist for a variable period, is posing new challenges to the health system, but few studies are available in India that examine the post-COVID-19 syndrome, that is, 6 months and beyond COVID-19 infection. This study aimed to find the prevalence and determinants of post-COVID-19 syndrome among patients 6 months and beyond their infection. **Methodology:** This cross-sectional study was conducted among 300 patients who were admitted and discharged from Government Medical College, Thrissur, at least 6 months before with a diagnosis of COVID-19 infection. The data collection was performed using a semi-structured interview schedule through a telephonic interview. The analysis was performed using the Statistical Package for the Social Sciences (SPSS) software. **Results:** 21% of the patients studied had at least one persistent symptom at the end of 6 months, and 4.1% had more than one symptom. Among the symptoms persisting most commonly were fatigue (11%) and dyspnea (7.7%). Other than persisting symptoms, 21% of patients developed exertional dyspnea and 19% developed sleep disturbances during the 6 months after discharge. The factors that were associated with persistent symptoms in univariate analysis were increasing age, presence of chronic obstructive pulmonary disease (COPD), presence of chronic kidney disease (CKD), and admission to the intensive care unit (ICU). **Conclusion:** The study concludes that one-fifth of the patients still suffer from post-COVID-19 syndrome even 6 months after the COVID-19 infection. Our health systems should be prepared for the long-term management of COVID-19-infected people and prepare policies for the same.

Keywords: Kerala, long-term COVID-19 syndrome, persistent COVID-19, post-COVID-19 syndrome

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious

disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been more than 4 years since the first case of COVID-19 was reported, and still, this pandemic remains a challenge to our healthcare system and affects the well-being of the whole world. As of August 2023, over 769 million confirmed cases and over 6.9 million deaths have been reported globally due to COVID-19.^[1] In the same period, India has reported a total of 44 million confirmed cases and about 5 lakh deaths.^[2]

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Current knowledge on COVID-19 has shown that a majority had only mild disease, but a few could go from severe disease to even death. The infection-to-hospitalization ratio (IHR), defined as the percentage of infected individuals who are hospitalized, is approximately 2.1%.^[3] In most of the cases, the patient experiences complete resolution of symptoms within 2–6 weeks.

A proportion of those infected with SARS-CoV-2 experience long-term symptoms. The World Health Organization (WHO) has developed a working clinical case definition for the post-COVID-19 condition. The post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.^[4] Patients usually present with persisting symptoms, such as fatigue and shortness of breath, or new-onset symptoms, such as cognitive dysfunction and sleep disturbances.^[5] It has been found that post-COVID-19 effects can happen even in people who have only suffered mild COVID-19 infection.^[6] The incidence of post-COVID-19 syndrome among patients who have received outpatient or home-based management has been found to be between 10% and 35%.^[7,8] Evidence from an Indian setting has shown an incidence of post-COVID-19 symptoms in around 9.9% of patients beyond 12 weeks after recovery from acute infection.^[9] The evidence regarding post-COVID-19 syndrome, its magnitude with time, determinants, and ways to manage it is going to evolve as time passes by. Thus, there is a need to better understand the clinical spectrum and long-term course of this clinical entity.

Prolonged health problems among those who have recovered from an acute infection, such as COVID-19, are posing a challenge to our health system, which has already been burdened by the pandemic. With millions of people being affected by COVID-19, even a small percentage of them developing post-COVID-19 conditions for a long time will have a serious effect on society and public health systems, with many people in need of long-term follow-up, management, and support, including rehabilitation. In Kerala, the government had to set up post-COVID-19 clinics in peripheral centers to address the long-term effects of COVID-19.^[10] The need for such exclusive clinics to tackle these health problems largely points toward the importance of this entity of post-COVID-19 syndrome. Also, there is a lack of studies on long-term COVID-19 or post-COVID-19 syndrome, especially 6 months and beyond primary infection, from healthcare settings in South India. Thus, it is indeed an area to research and bring out a clearer picture of this syndrome so that we can have evidence-based planning and prioritization of our healthcare resources, besides contributing to a better understanding of the long-term natural history of COVID-19. This will also act as a guideline for primary healthcare physicians on what to expect among long-term post-COVID-19 patients.

Thus, the principal aim of this study was to determine the proportion of patients who have persistent symptoms or have

developed new symptoms 6 months after COVID-19 infection and to determine the factors associated with it, among those who have been discharged from a tertiary care center in South India.

Materials and Methods

This cross-sectional study on long-term COVID-19 syndrome was conducted at Government Medical College, Thrissur, a tertiary care institution in the southern state of Kerala. The data collection was performed between October 2021 and January 2022 among those who were admitted and discharged from the hospital at least 6 months ago. The study was approved by the Institutional Ethics Committee as per the letter IEC/GMCTSR/189/2021 dated 6.10.2021.

Sample size

As per the study conducted by Dominik Menges *et al.*^[11] in Switzerland, 26% of the patients had persistent symptoms or were unwell 6–8 months post-infection. Applying it to the formula $4pq/d^2$, taking 26% as p , $Q = 1-p$, an alpha error of 0.05, and an absolute precision of 5%, the sample size was calculated to be 296.

In the Government Medical College, Thrissur, the details of all COVID-19 patients admitted to the hospital, including their mobile number, were collected as a hospital policy. The study was conducted among patients who were discharged from the hospital at least 6 months before with a diagnosis of COVID-19 infection and were above the age of 18 years. The data collection was performed using a semi-structured interview schedule over the phone. In the first part of the interview, the investigator explains to the patient the objectives of the study and asks for telephonic consent, which is recorded. He was also given the assurance that the details he provided would not be used for any other purpose. The information that the call was being recorded was also intimated to the participants. Then, the interview moves to the second part only if the person gives consent. In other cases, the person is excluded and the next person on the list is called. The semi-structured interview consisted of questions regarding the sociodemographic details of the person, clinical details while in the hospital, and persistent or new symptoms as on the date of the interview. Thus, a total of 321 people were contacted over the phone, 21 did not give consent for the study and were excluded, and the final sample size was 300.

Once the data were collected, they were properly coded and entered in Microsoft Excel. Further analysis was performed using the software Statistical Package for Social Sciences (SPSS) version 16.0. The persistence of symptoms at 6 months was expressed as proportions and confidence intervals. For finding out the factors associated with the persistence of symptoms, the dependent variable taken was the persistence of at least one of the symptoms. The Chi-square test was used to find the association of the persistence of symptoms with other factors. The P value of less than 0.05 was taken as statistically significant. The factors that were found to be significant in univariate analysis

were also analyzed using binary logistic regression using the enter method.

Results

Among the 300 people included in the study, the mean age was 44.95 years, with a standard deviation of 15.5 years. There was almost an equal representation of males and females in the study sample (52.7% and 47.3%). The age group with the highest representation in the study sample was 45–60 years, followed by 30–45 years (30.3% and 30%) [Table 1]. 24.3% of the population had an educational qualification of graduate and above. The majority (72.3%) had studied up to high school or above. As far as the occupation of the study group is concerned, 35% were unemployed and 46.7% were skilled or unskilled laborers [Table 1].

74.7% of the total studied had no persistent symptoms at the end of 6 months of COVID-19 infection, but 21% had at least one persistent symptom and 4.4% had more than one symptom persisting [Figure 1].

Of the symptoms persisting, the most common ones were fatigue (11%) and dyspnea (7.7%). Apart from persistent symptoms, some patients developed new symptoms that were not present during the COVID-19 infection. Apart from the persistent symptoms, some patients developed some new symptoms, which were not present before the COVID-19 infection. Among them, the most common ones were exertional dyspnea (21%) and sleep disturbances (19%) [Table 2].

69.7% of patients perceived their current physical health as the same as pre-COVID-19, but 30.3% perceived their physical health to be slightly worse or definitely worse than pre-COVID-19 [Figure 2].

It was also found that the persistence of symptoms beyond 6 months of COVID-19 positivity was associated with increasing age, with 30.2% of those above 60 years having at least one symptom persisting compared with 5.4% among those below 30 years. It was also associated with comorbidities, such as chronic obstructive pulmonary disease (COPD), where 77.8% had persistence of symptoms compared with 23.7% among those

without COPD. Persistence was also associated with chronic kidney disease (CKD), where 63.2% of those with CKD had persistence compared with 22.8% of those without. Among

Table 1: Basic demographic characteristics of the study population

Variable	Frequency	Percentage
Age group		
<30 years	56	18.7%
30–45 years	90	30%
45–60 years	91	30.3%
>60 years	63	21%
Gender		
Male	158	52.7%
Female	142	47.3%
Education		
Graduate/PG	73	24.3%
Higher secondary	60	20%
High school	84	28%
Primary/middle school	79	26.3%
Illiterate	4	1.4%
Occupational status		
Professional/semi-professional	21	7%
Clerk/shopkeeper/farmer	34	11.3%
Skilled/semi-skilled	62	20.7%
Unskilled	78	26%
Unemployed/retired	105	35%

Table 2: Symptoms persisting in post-COVID-19 patients

	Patients having persistent symptoms >6 months or new symptoms (n (%))
Fatigue	33 (11%)
Dyspnea	23 (7.7%)
Cough	12 (4%)
Myalgia	8 (2.7%)
Joint pain	8 (2.7%)
Pedal edema	7 (2.3%)
Others (decreased appetite, vertigo, headache, chest pain)	8 (2.7%)
New symptom (not present during hospital admission): exertional dyspnea	64 (21.3%)
Sleep disturbances (decreased, broken, delayed onset)	57 (19%)

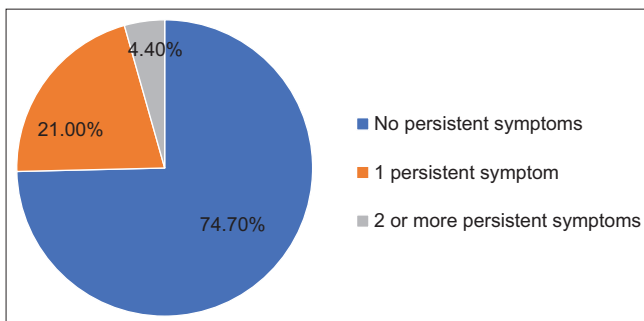


Figure 1: Persistence of symptoms in the study population

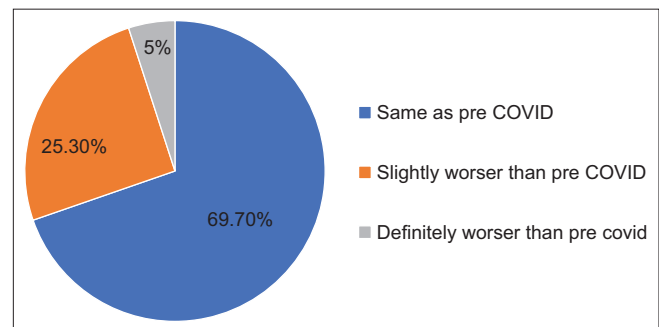


Figure 2: Patient's perception of current health by study population

those who were admitted to the intensive care unit (ICU), 64.3% had persistence compared with 23.4% among those who were in wards [Table 3].

Those factors that were found to be statistically significantly associated with the persistence of symptoms in the Chi-square test were also analyzed using binary logistic regression. In regression analysis, increasing age group (odds ratio: 2.33 (95% confidence interval (CI): 1.03–5.26)), presence of COPD in the patient (odds ratio: 9.64 (95% CI: 1.54–60.24)), presence of CKD (odds ratio: 4.5 (95% CI: 1.57–13.02)), and admission to an ICU (odds ratio: 5.03 (1.45–17.53)) were found to be significant predictors of the persistence of symptoms beyond 6 months post-COVID-19 infection.

Discussion

In the current study, the proportion of patients who had at least one persistent symptom at 6 months was 21% and 4.4% had more than one symptom. This is lower than what was reported in the study conducted by Max Augustin *et al.*^[12] in Germany where the proportion of COVID-19 patients who

had post-COVID-19 syndrome at 4 months and 7 months after symptom onset was 27.4% and 34.8%, respectively. In another study by Jennifer K. Logue *et al.*^[13] in the United States, the proportion of patients with at least one symptom persisting at 6 months after discharge from the hospital was 32.8%, whereas 13.6% of people had more than three symptoms persisting. Yet, in another study from Italy by Maddalena Peghin *et al.*^[14] the proportion of those with post-COVID-19 syndrome 187 days post-symptom onset was 40.2%. As per the study conducted by Deepa *et al.* in an urban area of north Kerala, the prevalence of post-COVID-19 syndrome was found to be 42.2%.^[15] Compared to these studies, the present study had a slightly lower prevalence of post-COVID-19 syndrome. Still, it can be seen that even 6 months after the COVID-19 infection, approximately one-fourth of the patients still had persistent symptoms, which could have long-term implications both with respect to the health resources required for post-COVID-19 management and current policies for the same.

As per the current study, the most common symptoms persisting at the end of 6 months were fatigue (11%), dyspnea (7.7%), and cough (4%). This is similar to the study conducted by Ahmet Naci Emecen in Turkey, where at the end of 6 months of follow-up

Table 3: Association of the persistence of symptoms with clinicodemographic factors

Exposure factors	Symptoms persisted n (%)	Symptoms not persisted n (%)	Chi-square	P
Age group				
<30	3 (5.4%)	53 (94.6%)	20.011	0.00
30–45	20 (22.2%)	70 (77.8%)		
45–60	34 (37.4%)	57 (62.6%)		
>60	19 (30.2%)	44 (69.8%)		
Any comorbidity				
Yes	58 (38.7%)	92 (61.3%)	28.195	0.00
No	18 (12%)	132 (88%)		
Diabetes mellitus				
Yes	32 (39%)	50 (61%)	11.182	0.001
No	44 (20.2%)	174 (79.8%)		
Hypertension				
Yes	34 (41.5%)	48 (58.5%)	15.521	0.00
No	42 (19.3)	176 (80.7%)		
CAD				
Yes	8 (47.1%)	9 (52.9%)	4.497	0.034
No	68 (24%)	215 (76%)		
CVA				
Yes	8 (47.1%)	9 (52.9%)	4.497	0.034
No	68 (24%)	215 (76%)		
COPD				
Yes	7 (77.8%)	2 (22.2%)	13.491	0.00
No	69 (23.7%)	222 (76.3%)		
CKD				
Yes	12 (63.2%)	7 (36.8%)	15.343	0.00
No	64 (22.8%)	217 (77.2%)		
Oxygen support in the hospital				
Yes	52 (34%)	101 (66%)	12.361	0.00
No	24 (16.3%)	123 (83.7%)		
ICU admission				
Yes	9 (64.3%)	5 (35.7%)	11.780	0.001
No	67 (23.4%)	219 (76.6%)		

the most common symptoms persisting were fatigue (9.03%), muscle and body ache (5.13%), and dyspnea (3.06%).¹¹⁶ In yet another study conducted by Nalinakumari Kesavan Nair Anjana *et al.*¹¹⁷ in Thiruvananthapuram, among 154 patients discharged from COVID First Line Treatment Centre (CFLTC) at the end of 3 months, 5.8% still had fatigue, 5.8% had headache, 3.2% had myalgia, and 2.5% had joint pain, but unlike these studies some studies have reported a high prevalence of fatigue among post-COVID-19 patients at 6 months of follow-up like J. González-Hermosillo *et al.*¹¹⁸ in Mexico among 130 patients who reported a prevalence of fatigue of 46.9%.

It was interesting to note that during the 6 months of follow-up period in the current study 21.3% developed exertional dyspnea and sleep disturbances (19%), which were not present before or during the COVID-19 infection. Alberto Fortini *et al.*¹¹⁹ in Italy also reported similar findings, with 37.3% having exertional dyspnea and 28.3% having insomnia 3–6 months after COVID-19 infection. Sleep disturbances in long-term COVID-19 syndrome have also been reported by Mario Mekhael *et al.* and Evgenia Kalamara, who both reported that both total sleep time and deep sleep time were decreased in patients with long-term COVID-19.^{120,21} The study results show that even at the end of 6 months a significant number of the population have not completely recovered from the COVID-19 infection and many have a new onset of symptoms, which were not present before or during the COVID-19 infection. Considering the sheer number of people infected with COVID-19 around the world, the persistence of such symptoms or new symptoms, such as exertional dyspnea and sleep disturbances, for an extended period of time could substantially hamper work efficiency and impact the net productivity and well-being of a large population.

Among the 300 patients who were part of the study, 30.3% of people perceived their health to be slightly or definitely worse than pre-COVID-19 condition. In a study conducted by Vincent Tarazona in France, COVID-19 patients even 1 year post-discharge had a much lower health-related quality of life than control when assessed using the EuroQol-5 Dimension scale (EQ-5D-5L).¹²² Similar findings showing lower health-related quality of life among long-term COVID-19 patients have been reported in multiple studies around the world.^{123,24}

The current study shows that older age groups have a higher risk of developing long-term COVID-19 syndrome compared with younger ones. Imad M. Tleyjeh *et al.*¹²⁵ in Saudi Arabia reported age more than 50 as a significant predictor for lack of return to normal 4–6 months after COVID-19 infection with an adjusted odds ratio of 10.05 compared with younger age groups. The association between increasing age and long-term COVID-19 syndrome has also been shown in other studies conducted by Mark W Tenforde in the United States and Roy H. Perlis in Columbia.^{18,26}

The current study found that the long-term COVID-19 syndrome is closely associated with the presence of comorbidities. This is

similar to the study conducted by Imad M. Tleyjeh *et al.*¹²⁵ who found that the presence of diabetes mellitus, hypertension, or liver disease was an important predictor of long-term COVID-19 syndrome. The relationship between comorbidities and long-term COVID-19 syndrome has also been shown in the meta-analysis conducted by Kin Israel Notarte *et al.*¹²⁷ A similar association was also shown by M. C. Arjun *et al.*¹²⁸ in India, who showed that the presence of a preexisting medical condition was a risk factor for long-term COVID-19 syndrome with an adjusted odds ratio of 2.1. In a country like India, where the prevalence of comorbidities, such as hypertension and diabetes, is high, this could have far-reaching implications in the long run.

The results of the current study showed that ICU admission was a significant predictor of symptoms that persisted 6 months following the COVID-19 infection. The multivariate analysis of a study conducted among 449 patients in Italy by L Boglione *et al.*¹²⁹ revealed ICU admission to be one of the independent predictors of long-term COVID-19 syndrome. Research by Aliae AR Mohamed Hussein *et al.* in Egypt and Ali Akbar Asadi-Pooya *et al.* in Iran also revealed an association between long-term COVID-19 syndrome and ICU admission.^{30,31}

Conclusions and Recommendations

The current study shows that the health effects of COVID-19 infection linger even after 6 months post-COVID-19 infection, either as persistent symptoms or as new symptoms, such as exertional dyspnea or sleep disturbances. The authors recommend a long-term comprehensive management strategy for post-COVID-19 health issues, especially among primary health physicians.

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Conflicts of interest

There are no conflicts of interest.

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