

Persistence of Symptoms after Acute COVID-19 Infection- An Experience from a Tertiary Care Centre in South India

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ABSTRACT

Introduction: Coronavirus Disease-19 (COVID-19) pandemic is posing a challenge not only with sheer number of people infected but also with the large number of patients with persistent symptoms of COVID-19 infection. A proper understanding of the magnitude and associated factors of persistent COVID-19 symptoms will go a long way in planning treatment and control strategies.

Aim: To determine the proportion of patients who have persistent symptoms post acute COVID-19 infection and to determine the factors associated with it, among those who have been discharged from Government Medical College, Thrissur, Kerala, India.

Materials and Methods: The current cross-sectional study was conducted among 335 patients who were admitted and discharged with COVID-19 infection in Government Medical College, Thrissur, Kerala, a tertiary care institution in southern India between December 2020 and February 2021. They were contacted through a telephonic interview 28 days from symptom onset through a semi-structured interview schedule. The questions included basic demographic details, symptomatology

at admission, persistent symptoms at 28 days after onset and other clinical details including comorbidities. For defining post COVID-19 symptom persistence National Institute for Health and Care (NICE) guidelines were used. Association between persistent symptoms and selected factors was done by Chi-square test.

Results: Out of the 335 patients, the persistence of symptoms of COVID-19 infection after 28 days of symptom onset was 221 (66%) (CI 60.7-79.8). Persistence of two or more COVID-19 symptoms after 28 days of onset was seen in 120 (35.8%). The most common persistent symptoms among the patients were fatigue in 109 (32.5%) of people followed by dyspnoea in 77 (23%), cough in 45 (13.4%) and myalgia in 37 (11%) patients. Highest persistence was seen in Category C patients where symptoms were persisting in 75%. Persistence was also higher in those with Diabetes Mellitus (DM), those who received oxygen support and those who were in Intensive Care Unit (ICU) or on ventilator and the association was statistically significant (p -value < 0.05).

Conclusion: The study shows that two-third of patients still continues to have persistent symptoms even after 28 days of symptom onset. Health systems should be prepared to face the consequences of morbidities caused by post COVID-19 syndrome.

Keywords: Long coronavirus disease syndrome, Semi structured interview, Telephonic interview

INTRODUCTION

The COVID-19 which had its origins in Wuhan, China in December 2019, has now spread to all continents and has been declared as a global pandemic on March 11 by the World Health Organisation (WHO) [1]. As of March 2021, India had over 11 million cases and over 1.6 lac deaths due to COVID-19 [2]. Since its inception COVID-19 has posed an unprecedented challenge to human health and economy especially to countries like India [3]. The first COVID-19 case in India was reported in Kerala in January 2020 [4]. Even though the number of cases were very less in Kerala in the initial phase, it surged since July 2020 and have now reached a cumulative number of more than 1.1 million cases with over 4000 deaths [5].

Acute COVID-19 infection presents as mild to moderate respiratory illness and most people recover without requiring special treatment. But in certain groups like older people, those with comorbidities like cardiovascular disease, diabetes, Chronic Obstructive Pulmonary Disorder (COPD) and cancer COVID-19 can lead to serious complications like pneumonia, Acute Respiratory Distress Syndrome (ARDS) and death [6,7]. While the world is still going through the COVID-19 pandemic and its implications with high occupancy of hospital beds and intensive care units, another challenge that has emerged is the health problems of those who have been discharged after COVID-19 infection. It has been observed that some patients

continue to experience symptoms related to COVID-19 after the acute phase of infection [8].

In a study conducted in Italy, only 13% of the previously hospitalised COVID-19 patients were completely free of any COVID-19-related symptoms, while 32% had one or two symptoms and 55% had three or more symptoms 60 days after onset of the first COVID-19 [8]. Various studies from around the globe have reported proportion of post COVID-19 infection. Patients having at least one persisting symptom between 30 to 60 days post symptom onset to be between 72.7% and 87.4% [8-10]. Most common persistent symptom after acute COVID-19 infection were fatigue and dyspnoea [9]. Persistent symptoms were even seen in patients with mild symptoms during their acute COVID-19 infection [11].

These persistent symptoms post-acute COVID-19 infection will definitely pose newer challenges to patients, healthcare providers, administrators and public health practitioners. Government of Kerala, India has already started the post COVID-19 clinics since November 2020 considering the number of people likely to be affected by persistent COVID-19 symptoms [12].

Evaluating the short, medium and long-term impact of COVID-19 disease is absolutely necessary to understand the complete natural history of the disease, help the clinicians in decision making about the requirement of in-patient or post-discharge treatment and

rehabilitation. The current study will help public health practitioners, clinicians and policymakers into the symptoms that they should be prepared to face in post COVID-19 and general clinics in the coming months and years. It will also throw light into the possible factors which are associated with persistent post-acute COVID-19 infection.

Thus, the principle aim of the present study was to determine the proportion of patients who have persistent symptoms post acute COVID-19 infection and to determine the factors associated with it, among those who have been discharged from Government Medical College, Thrissur.

MATERIALS AND METHODS

The current cross-sectional study was conducted in Government Medical College, Thrissur a government-run tertiary care institution in the southern state of Kerala, India, among the patients discharged with a diagnosis of COVID-19 infection. The data collection and analysis period were between December 2020 to February 2021. The study was approved by the Institutional Ethical Committee (per letter IEC/GMCTSR/085/2020 dated 05.12.2020) and informed consent was obtained.

Inclusion criteria: All patients who have been discharged from the hospital prior to December 2020 and has completed 28 days from their symptom onset or COVID-19 positivity were included in the study.

Exclusion criteria: Those who were not willing for the study, asymptomatic patients, lactating females, bed ridden patients and expired patients were excluded from the study.

Sample size calculation: The sample size was calculated using the formula $4pq/d^2$. As per the study conducted by Carfi A et al., in Italy the proportion of patients with at least one persistent symptom was 32.2% [8]. Taking this as P and an error of 5% and beta error of 20% and absolute precision of 5% the minimum sample size was calculated as 335.

The primary details of all patients admitted in the hospital with COVID-19 infection including phone number were collected as a part of hospital policy.

The method of data collection was by a telephonic interview among those who satisfied the inclusion criteria. The interview consisted of two parts. First part the investigator explained about the study details and asked permission from the study participant to take part in the study. He was also given the assurance that the details he provides will not be used for any other purpose. The information that the call was recorded was also intimated to the participants. If the person was willing for the study the second part of the interview was initiated. This contained questions on the symptoms while in the hospital, history of persistence of symptoms and details of the same at the end of 28 days after symptom onset. Details regarding their general health condition and comorbidities were also asked. The interview was closed with greetings from the data collection team.

Thus, a list of 373 were made by the team from the hospital records for data collection. Out of them, 15 did not give consent for the study, another 23 could not be contacted even after repeated attempts and were excluded from the study. Even though the team tried to contact every patient in the study 28 days after symptom onset, in some cases, interview could be done only by day 35.

For defining post COVID-19 health conditions, NICE with National Health Scheme (NHS) England guidelines were used [13]. It describes acute COVID-19 as signs and symptoms of COVID-19 for up to four weeks. If symptoms persist beyond four weeks up to 12 weeks it has been defined as ongoing symptomatic COVID-19. In those in which signs and symptoms continue for more than 12 weeks and are not explained by an alternative diagnosis is defined as having post COVID-19 syndrome. Symptoms at presentation in the study was classified as category A, B and C according to severity of symptoms based on the guidelines prepared by Government of Kerala, India [14].

STATISTICAL ANALYSIS

The data was properly coded and was entered in Microsoft Excel. Further analysis was done using software Statistical Package for Social Sciences (SPSS) version 16.0. Persistence of symptoms was expressed as proportions and confidence intervals. For finding out the factors associated with persistence of symptoms, the dependent variable taken was persistence of at least one of the most common morbidities namely fatigue, dyspnoea, myalgia or cough. Chi-square test was used for finding out association of persistence of symptoms with other factors. The p-value of less than 0.05 was taken as statistically significant.

RESULTS

Among the 335 people included in the study, the mean age was 50.7 ± 15.7 years. There was almost an equal representation of males and females in the study 174 (51.9%) and 161 (48.1%). The age group with the maximum number of people in the study was 40-60 years 151 (45.1%) followed by 20-40 years 94 (28%). Most of the study participants had an education above high school 107 (31.9%) and 68 (20.3%) were graduates or above. As far as the occupation was concerned, majority 145 (43.3%) were unemployed, 58 (17.3%) were skilled workers. The basic demographic details have given in [Table/Fig-1].

Participant characteristics	Frequency	Percentage
Gender		
Male	174	51.9
Female	161	48.1
Age group (years)		
20-39	94	28
40-59	151	45.1
60-79	81	24.2
80 and above	9	2.7
Educational status		
Upto primary school	29	8.7
Middle school	79	23.6
High school	107	31.9
Intermediate	52	15.5
Graduates and above	68	20.3
Occupational status		
Professional/ Semi professional	42	12.5
Clerks and others	50	14.9
Skilled workers	58	17.3
Manual labourers and daily wage workers	40	12
Unemployed	145	43.3

[Table/Fig-1]: Demographic characteristics of the study population (N=335).

As far as co-morbidities were concerned, 114 (34%) of the study group were suffering from DM, 84 (25%) were hypertensives and 57 (17.1%) did not have any kind of comorbidities. The mean duration of stay in the hospital for the study group was 10.6 days ± 9.46 days.

The proportion of patients with ongoing symptomatic COVID-19 infection i.e., persistence of COVID-19 symptoms after 28 days of symptom onset was 221 (66%) (CI 60.7-79.8). And, 120 (35.8%) had persistence of two or more COVID-19 symptoms after 28 days of onset, 114 (34%) were completely relieved of their symptoms. The data on number of symptoms persisting in study population has given in [Table/Fig-2].

Symptoms	Frequency (n)	Percentage
No symptoms persisted	114	34.0
Persistence of one symptom	101	30.2
Persistence of two or more symptoms	120	35.8

[Table/Fig-2]: Number of symptoms which persisted in the Study Population on day 28 (N=335).

The most common persistent symptoms among the patients were fatigue in 109 (32.5%) of people followed by dyspnoea in 77 (23%), myalgia in 37 (11%), cough in 45 (13.4%) and joint pain in 28 (8.4%). The full data on symptoms in hospital and persistent symptoms is shown in [Table/Fig-3].

Symptoms	Patients having symptoms while in hospital, n (%)	Patients having persistent symptoms on day 28, n (%)
Fatigue	195 (58.2)	109 (32.5)
Dyspnoea	150 (44.8)	77 (23)
Cough	141 (42.1)	45 (13.4)
Myalgia	105 (31.3)	37 (11)
Joint pain	57 (17.0)	28 (8.4)
Insomnia	46 (13.7)	23 (6.9)
Dysgeusia	95 (28.4)	21 (6.3)
Anosmia	46 (13.7)	20 (6)
Fever	171 (51.0)	14 (4.2)
Headache	80 (23.9)	13 (3.9)
Chest pain	36 (10.7)	9 (2.7)
Sputum	52 (15.5)	9 (2.7)
Loss of appetite	44 (13.1)	8 (2.4)
Pedal oedema	17 (5.1)	8 (2.4)
Diarrhea	46 (13.7)	6 (1.8)
Inability to concentrate	8 (2.4)	6 (1.8)
Sore throat	48 (14.3)	5 (1.5)
Vertigo	22 (6.6)	5 (1.5)
Rhinitis	47 (14)	2 (0.6)
Others	35 (10.4)	6 (1.8)

[Table/Fig-3]: Comparison of symptoms in hospital and persistent symptoms on day 28 (N=335).

It was found that the persistence of post COVID-19 symptoms was statistically significantly associated with initial category of symptoms. Highest persistence was seen in Category C patients where symptoms were persisting in 93 (75%) of patients compared to those patients in Category A or B [27 (57.6%) and 63 (38.4)]. It was also found to be associated with presence or absence of DM where 75 (65.8%) patients persisted the symptoms and 106 (48%) did not and symptoms persisted in those who did or did not received oxygen support in the hospital were 89 (73.6%) and 92 (43%) [Table/Fig-4].

DISCUSSION

The majority of patients affected by COVID-19 were above the age of 40 years 241 (72%). A two-third of patients or population had an education above high school or above 230 (67.7%). Most of the study population were unemployed 145 (43.3%). The most common comorbidity in the study population was DM (34%).

The proportion of patients with at least one persistent symptom post COVID-19 as per the current study was 66%. The findings are consistent with a study conducted by Carfi A et al., in a different setting, in Italy, where 32% had one or two symptoms and 55% had three or more persistent symptoms when patients were assessed at a mean of 60 days after onset of symptoms [8]. In another study in Spain among 277 patients, 77 days after disease onset the persistence was found to be 50.9%. The sheer proportion of symptom persisters makes the follow-up and proper treatment of post COVID-19 cases to be a herculean task considering the huge number of people infected in the country [15]. Similar study in Mexico among post COVID-19 patients, 84% had persistent symptoms between 30-60 days after their symptom onset [16]. In another study from United Kingdom, nearly a third of individuals who were discharged from hospital after acute COVID-19 were readmitted (14060 of 47780) and more than 1 in 10 (5875) died after discharge at a mean follow-up of 140 days [17].

Exposure factors	Symptoms persisted n (%)	Symptoms not persisted n (%)	Chi-square	p-value
Category of symptoms at admission				
Category A	27 (57.6)	20 (42.6)		
Category B	63 (38.4)	101 (61.6)	38.3	0.001
Category C	93 (75)	31 (25)		
Diabetes mellitus (co-morbidity)				
Yes	75 (65.8)	39 (34.2)	9.62	0.003
No	106 (48)	115 (52.0)		
Usage of supportive measures during hospital admission				
Oxygen support in hospital				
Yes	89 (73.6)	32 (26.4)	29.07	0.001
No	92 (43.0)	122 (57.0)		
ICU admission				
Yes	23 (85.2)	4 (14.8)	11.47	0.001
No	158 (51.3)	150 (48.7)		
Ventilator admission				
Yes	6 (85.71)	1 (14.28)	6.34	0.042
No	175 (53.4)	153 (46.6)		

[Table/Fig-4]: Factors associated with persistence of symptoms in study population (N=335).
p<0.05 statistically significant

As per the current study, none of the patients had fever or any signs or symptoms of active illness on day 28. Most common symptoms identified were fatigue in 109 (32.5%) of people followed by dyspnoea in 77 (23%), cough in 45 (13.4%) and myalgia in 37 (11%). As per the study conducted by Jacobs LG et al., in USA, 55% of the post COVID-19 patients had persistent fatigue, 50.6% had myalgia and 45.3% had shortness of breath [9]. In another study conducted in UK by Mandal S et al., 53% had persistent breathlessness, 34% cough and 69% had fatigue 54 days post discharge [18]. Compared to these studies in Europe and US, the current study reports a lower prevalence of those with persistent symptoms. These differences could be due to the difference in study settings, the type of study participants and the time interval after onset of symptoms when assessment was made. But some studies have even reported persistence of these symptoms even 120-180 days after their symptom onset which is alarming [11,19,20]. This evidence shows the importance of follow-up of all patients with COVID-19 infection so that appropriate treatment can be initiated at the earliest. With huge numbers infected in many continents with symptoms persisting on a long term, it is time to think about long term policies and treatment guidelines for this group of patients. This added to the information that another infection caused by coronaviruses i.e., SARS, persistence of symptoms has been found for years [21,22]. As per the current study, persistent symptoms post COVID-19 were significantly associated with DM in patients. Diabetes is a disease in which the affected person is more susceptible to a wide range of infections [23]. Multiple studies have shown the relationship of diabetes as prognostic factor of COVID-19 infection including mortality [24,25]. The finding of the current study showed that DM is one of the most important prognostic factor not only during acute COVID-19 infection but also for long COVID-19 syndrome.

Another factor that was associated with COVID-19 symptom persistence was severity of COVID-19 at presentation. Government of Kerala had classified the COVID-19 patients as Category A, B and C as per severity [14]. Even though higher persistence was seen in category C severe patients it has to be noted that even among mild cases, 57.6% had persistent symptoms. Similar results have been found in the study from US where they found no significant difference between proportion of patients with persistent symptoms in the uncomplicated and severe COVID-19 cases when the assessment

was done after 3-4 months of symptom onset [11]. Given the fact that majority of COVID-19 infections were asymptomatic or mild, a significant number of patients with persistent symptoms in the mildly symptomatic group could have important implications in policies related to post COVID-19 management.

Limitation(s)

As the study was done by telephonic interviews, there could be an element of recall especially among elderly participants. Since the symptoms were evaluated only through history, there could be subjectivity in reporting.

CONCLUSION(S)

The study concludes that the majority of patients have persistent symptoms of COVID-19 infection at 28 days post onset of symptoms. The persistence of symptoms in such a huge number of people will definitely pose challenges not only to the treating team but also to the planners and policy makers. The follow-up of post COVID-19 patients at regular intervals should be done so that symptoms can be identified early and treatment can be initiated. The study also recommends the opening of post COVID-19 clinics at primary, secondary and tertiary levels for treatment of medium term and long-term health problems.

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