

Manifestations and risk factors of post COVID syndrome among COVID-19 patients presented with minimal symptoms – A study from Kerala, India

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ABSTRACT

Background: COVID 19 is associated with the development of post COVID syndrome usually manifested as fatigue, anxiety, joint pain, headache, chest pain, dementia, depression, and dyspnea. Documented evidence of post COVID syndrome among patients with asymptomatic or mild infections, especially from India is less. **Methodology:** A community based prospective cohort study was conducted among 154 patients admitted in CFLTCs of coastal Thiruvananthapuram, Kerala during May-August 2020. They were enrolled at the time of their admission to CFLTCs and were followed up for three months after discharge. The discharged patients were followed up at regular intervals of three weeks and three months by telephonic interview using a structured proforma. **Results:** Out of the 154 patients followed up, 57 (37%) were men and 97 (63%) were women. The mean (SD) age of study participants was 31.49 (18.4) years. At least one symptom was present in 120 (78.0%) patients at the time of admission. Cough (29, 18.8%), fever (26, 16.8%), headache (25, 16.2%), rhinitis (23, 14.9%) and sore throat (18, 11.7%) were the major symptoms reported at the time of admission. At the end of three weeks, 11 (7.1%) patients and at the end of three months 18 (11.7%) patients reported to have symptoms. Fatigue (5.8%), headache (5.8%) myalgia (3.2%) joint pain (2.5%) and exertional dyspnea (2.5%) were the predominant symptoms. Presence of fatigue, cough and breathlessness at the time of admission, and presence of another COVID positive family member were significantly associated with the appearance of post COVID symptoms. **Conclusion:** Post COVID syndrome is not uncommon in COVID 19 patients with minimal symptoms. Understanding long term consequences of COVID 19 is as important as management of acute COVID 19 due to its multisystem involvement and its implications on health and well-being.

Keywords: India, Kerala, mild symptoms, post COVID syndrome, risk factors

Introduction

COVID-19 caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) is primarily a respiratory disease.

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Received: 08-05-2021

Revised: 25-06-2021

Accepted: 29-06-2021

Published: 29-11-2021

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_851_21

Though most people with COVID-19 experience mild symptoms or moderate illness, approximately 10-15% of cases progress to severe disease, and about 5% become critically ill.^[1] Patients recover from COVID-19 usually after a period of 2 to 6 weeks.^[1] But chronic manifestations of COVID-19 infection has been evident and it has been seen that one in ten individuals may

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How to cite this article: Anjana NK, Annie TT, Siba S, Meenu MS, Chintha S, Anish TS. Manifestations and risk factors of post COVID syndrome among COVID-19 patients presented with minimal symptoms – A study from Kerala, India. J Family Med Prim Care 2021;10:4023-9.

continue to have symptoms even after three weeks, and some may suffer from symptoms for weeks to months.^[2] Post-acute COVID-19 is defined as a condition where manifestations of COVID 19 are extending beyond three weeks from the onset of symptoms and chronic COVID-19 as extending beyond 12 weeks.^[3,4] A multistate telephone interview of symptomatic SARS-CoV-2 patients aged 18 years and above revealed that 35% of patients had not returned to their normal state of health when interviewed 2–3 weeks after testing. Among patients belonging to the age group of 18–34 years with no comorbidities, 20% had not returned to their normal state of health.^[5] COVID-19 can result in prolonged illness, even among young adults without underlying chronic medical conditions.^[5] Post recovery manifestations were also reported in severe acute respiratory syndrome (SARS) attack in 2003 reflecting many symptoms such as fatigue, myalgia, depression, and weakness.^[6] Now we have accumulating evidence of persistence or emergence of symptoms and manifestations beyond acute SARS-CoV2 infection.^[7–12] The severity of post-COVID-19 manifestations was found to be related to the severity of COVID-19 and common manifestations were fatigue, anxiety, joints pain, continuous headache, chest pain, dementia, depression, and dyspnoea.^[11,13,14] Rare, yet severe manifestations included neurological, pulmonary and cardiac events.^[7,15,16]

Most of the studies so far published in this regard are on hospitalized patients with moderate to severe symptoms. Documented evidence of post COVID syndrome among patients with asymptomatic or mild infections, especially from India is less. One of the earliest identified community clusters of COVID 19 in India was from the coastal region of Kerala state. The health system of Kerala responded to this crisis by various strategies including setting up COVID-19 first line treatment centers (CFLTC) to admit test positive persons who were either asymptomatic or with mild symptoms.^[17] This helped in limiting the spread of infection as well as providing appropriate care for such persons. Patients admitted to CFLTCs of coastal belt of Thiruvananthapuram district of Kerala provided an early cohort of asymptomatic and mild COVID 19 patients, which was an opportunity for long term follow up for documenting post COVID symptoms among this category of patients. This study aims to describe the post COVID-19 manifestations and its determinants among patients who were admitted to CFLTCs of the coastal belt of Thiruvananthapuram.

Methodology

Design, setting and study population

A community based prospective cohort study was conducted among patients admitted in CFLTCs of coastal Thiruvananthapuram, Kerala during May-August 2020. The coastal population of Kerala is distinct with an average population density of 1,111 people per sq km,^[18] which combined with the poorly ventilated and overcrowded housing conditions and close social interaction as part of their livelihood predisposes the community to intense and rapid disease transmission. Out of the 11 CFLTC's present in Thiruvananthapuram district at

the beginning of the study, two were located in the coastal area and were selected for the study. Participants were enrolled at the time of their admission to CFLTCs and were followed up for three months after discharge.

Following the outbreak of COVID 19 along the coastal belt, intensified testing was done based on two criteria. Patients who had influenza-like illness who presented to hospitals or detected by community survey were tested. Primary or secondary contacts of detected COVID-19 cases were kept either under home quarantine or at a facility provided by the government and were tested when they developed of any symptoms or after seven days from the day of last contact with the patient. Among the tested positives, asymptomatic or mildly symptomatic individuals were shifted to CFLTC for supportive management. Patients with severe symptoms or with any danger signs were shifted to a COVID hospital. Repeat testing on day ten was done among admitted patients and those tested negatives were discharged if they were clinically stable. All discharged patients satisfied uniform discharge criteria.

Sample size and sampling technique

We assumed a modest incidence proportion of 10% post COVID syndrome among mildly symptomatic COVID-19 infection, with absolute precision of 5% for calculating the sample size. 154 study participants were selected from the line list of patients admitted at the selected CFLTCs using simple random sampling. Inclusion criteria for the participant was a positive test result with RT-PCR or antigen test for COVID-19. Pregnant women and lactating mothers were not admitted to CFLTCs and hence not included in the study.

Data collection procedure

Data was collected using a structured proforma. The proforma had two parts. First part was used to collect socio-demographic variables, clinical presentation at the time of admission to treatment center, presence of any comorbidities, results of laboratory investigations, treatment given and treatment outcome at the hospital. The treating doctor was then contacted/case sheets were verified to complete the data collection.

Once the patient is discharged, he/she was followed up at regular intervals of three weeks and three months by three dedicated telephonic interviewers trained on telephonic data collection. Second part of the proforma was used to collect the follow up data. Presence of symptoms like fatigue, headache, myalgia, breathlessness, orthopnea, joint pain, dry cough, syncope, exertional dyspnea, sleep disturbances, chest pain at any time following discharge from the hospital and events like hospital admissions and death were recorded.

Ethical considerations

Approval from the Institutional Ethics Committee was obtained prior to the beginning of the data collection. (Ethics clearance certificate number-HEC.No. 07/70/2020/MCT). Permissions

from the District Medical Officer and the nodal officer in charge of the CFLTCs were taken prior to the study. Written informed consent was obtained from all the participants or responsible bystanders at the time of admission to the treatment center. All patient details were kept confidential. There was no financial burden to the patients.

Data analysis

MS Excel software was used for data entry and Statistical Package for the Social Sciences (SPSS) software version 25 (IBM Corp, Armonk, New York, United States) was used for data analysis. The proportion of patients who developed symptoms was expressed in percentage. Mean and standard deviation were used to express quantitative variables like age, length of hospital stay, time of onset of complications. Categorical variables like presence of symptoms, co-morbidities, presence of post COVID complications were expressed as proportions. Quantitative variables were compared using independent sample *t* test. Categorical variables were compared using Chi square test. Statistical significance was set at two-sided $P < 0.05$.

Results

Out of the 154 patients followed up, 57 (37%) were men and 97 (63%) were women. The mean (SD) age of study participants was 31.49 (18.4) years. Majority (50.6%) of the patients were in the age group of 18-45 years. One-fourth (39, 25.3%) of the study participants were aged below 18 years. Most of the patients, 109 (70.8%) were having minimal symptoms at the time of admission and reported as Category A by the treating physician and 43 (29.2%) were having moderate symptoms and were belonging to Category B. Two patients had significant symptoms (Category C) but were allowed to be treated at CFLTC as there were no co-morbidities or other danger signs. Among the 154 patients, 15 (9.7%) had any of the comorbidities. Hypertension was the most common co-morbidity reported among participants (4.5%) [Table 1]. At least one symptom was present in 120 (78.0%) patients. Mean (SD) length of hospital stay was 11.8 (2.13) days. Patients were kept at CFLTC for a minimum of 10 days as per the State's policy and the maximum duration of stay was 18 days. Testing was done on day 10 and those who were negative were discharged. A good proportion of

Table 1: Demography of study participants and symptomatology at the time of admission (n=154)

Variable	Category	Number of participants	Percentage
Gender	Male	57	37
	Female	97	63
Age category	<18 yrs	39	25.3
	18 to 45 yrs	78	50.6
	45 to 65 yrs	30	19.5
	>65 yrs	7	4.5
Categorization based on physician assessed severity of symptoms	A (no or mild)	109	70.8
	B (moderate)	43	27.9
	C (severe)	2	1.3
Comorbidities	Present	15	9.7
	Absent	139	90.3
Co-existing disease	Hypertension	7	4.5
	Cardiac disease	3	1.9
	Diabetes Mellitus	2	1.2
	Respiratory diseases	2	1.2
	Dyslipidemia	1	0.6
Symptoms at the time of admission to CFLTC	Present	120	77.9
	Absent	34	22.1
Symptoms at the time of admission to CFLTC	Cough	29	18.8
	Fever	26	16.8
	Headache	25	16.2
	Rhinitis	23	14.9
	Sore throat	18	11.7
	Myalgia	13	8.4
	Breathlessness	11	7.1
	Fatigue	5	3.2
	Chest pain	3	1.9
	Diarrhea	3	1.9
	Abdominal pain	2	1.3
	Nausea	1	0.6
	Skin rash	1	0.6
Medications during stay at CFLTC (Antibiotics)	Taken	27	17.5
	Not taken	127	82.5

them 63 (40.9%) had at least one family member in their house tested positive for COVID-19. Hence some had to stay back at CFLTC to take care of other infected family members.

Majority of the study participants (109, 70.8%) were asymptomatic or mildly symptomatic during the course of their stay at CFLTCs. Moderate symptoms were present in 43 (27.9%) individuals and severe symptoms were present only in two patients. Cough (29, 18.8%), fever (26, 16.8%), headache (25, 16.2%), rhinitis (23, 14.9%) and sore throat (18, 11.7%) were the major symptoms reported at the time of admission [Table 1]. Only 15 (9.7%) reported to have any kind of co-morbidities (details given in Table 1). Medications (antibiotics) were given to 27 (17.5%) of patients during admission. One patient received both antibiotics and antiviral. None of the patients were put on steroids or received oxygen or nebulization during the course of their stay at CFLTC. Development of moderate/severe symptoms was found to be significantly associated with the presence of comorbidities, ($P < 0.001$, OR = 12.85 (3.42-48.29).

The patients discharged from CFLTCs were followed up and at the end of three weeks, 11 (7.1%) patients reported to be symptomatic. Fatigue (5.8%), headache (4.5%), myalgia (2.5%), joint pain (1.9%) and exertional dyspnea (1.9%) were the most frequently reported symptoms. At the end of three months, 18 (11.7%) patients reported having symptoms. Fatigue (5.8%), headache (5.8%) myalgia (3.2%) joint pain (2.5%) and exertional dyspnea (2.5%) were the predominant symptoms. During the follow up period of three months, 22 (14.3%) patients had post COVID symptoms. Details are given in Table 2.

Univariable analysis was done to find out the factors associated with post COVID symptoms. Female gender was significantly associated with the presence of symptoms at the end of three weeks and three months. Presence of fatigue, cough and breathlessness at the time of admission was significantly associated with the appearance of post COVID events. The presence of a family member infected with COVID 19 was found to be significantly associated with the development of post COVID events. Table 3 shows the results of bivariable analysis.

Discussion

This study documents the incidence and risk factors of post COVID syndrome among asymptomatic or mildly symptomatic patients, admitted to CFLTCs of the coastal belt of Thiruvananthapuram, Kerala. We followed up 154 patients and assessed the presence of post COVID symptoms among them on day 21 and day 90. In this study, 7.1% and 11.7% of patients had at least one symptom during follow up on day 21 and day 90 respectively and 22 (14.3%) patients had the presence of symptoms any time during the follow up. In a multi-center cohort study, 7.4% of patients had symptoms after resolution of acute illness at 90 day follow up.^[19] The overall proportion of post COVID events was 14.3% in this study. But this is relatively a smaller proportion when compared with similar cohort studies

Table 2: Symptoms developed during follow-up (n=154)

Variable	Category	Number of participants (n=154)	Percentage
Symptoms during follow-up (Overall)	Present	22	14.3
	Absent	132	85.7
Symptoms at the end of 3 weeks	Present	11	7.1
	Absent	143	92.9
Symptoms at the end of 3 weeks	Fatigue	9	5.8
	Headache	7	4.5
	Myalgia	4	2.5
	Joint pain	3	1.9
	Exertional dyspnea	3	1.9
	Orthopnea	1	0.6
	Dry cough	1	0.6
	Absent	18	11.7
Symptoms at the end of 3 months	Present	136	88.3
	Absent	18	11.7
Symptoms at the end of 3 months	Fatigue	9	5.8
	Headache	9	5.8
	Myalgia	5	3.2
	Exertional dyspnea	4	2.5
	Joint pain	4	2.5
	Orthopnea	1	0.6
	Dry cough	1	0.6
	Absent	18	11.7

in Italy, France, China and the United Kingdom, which reported the presence of post COVID symptoms in 55% to 87.6% of the patients who required hospitalization during acute COVID 19 infection.^[10,20-22] In a systematic review and meta-analysis done, 80% of individuals with a confirmed COVID 19 diagnosis continue to have at least one overall effect beyond two weeks following acute infection. Not many well conducted studies are available on the development of post COVID symptoms in patients with minimal symptoms during acute COVID infection.

The most common post COVID symptom reported among COVID 19 survivors was fatigue, both at three weeks and three months follow up. Fatigue (58%) was the most common symptom of both acute and long term COVID and persisted even 100 days post symptom onset.^[23] In this study, fatigue, headache, and myalgia were the predominant symptoms on follow up at 3 weeks and 3 months similar to the findings in the systematic review and meta-analysis in which fatigue, headache, attention disorder, hair loss and dyspnea were the predominant long term symptoms.^[24] Muscle weakness, fatigue and sleep difficulties were identified in an ambidirectional cohort study done in China.^[22] A previous study from Ireland concluded that fatigue following SARS CoV 2 is not associated with initial disease severity and increasing age was significantly associated with fatigue.^[23] Post SARS fatigue has been reported in 40% of individuals one year after initial infection.^[25] It has been noted that there has been a significant and persistent reduction in exercise capacity following a COVID 19 infection which can clinically manifest as exertional dyspnoea.^[26] In a telephonic follow up study by Halpin *et al.*,^[21] which involved patients admitted in intensive care units as well as wards, it was found that fatigue, breathlessness and neuropsychological manifestations were the three predominant manifestations in patients.

Table 3: Factors Associated with Post-Acute COVID syndrome

Features	Category	Symptoms at 3 weeks		P	Odds ratio (95% CI)
		Present (n=11), n (%)	Absent (n=143), n (%)		
Gender	Male (n=57)	1 (1.8)	56 (98.2)	0.05	0.15 (0.02-1.25)
	Female (n=97)	10 (10.3)	87 (89.7)		
COVID positive family member	Present (n=63)	8 (12.7)	55 (87.3)	0.05	4.3 (1.1-16.8)
	Absent (n=91)	3 (3.3)	88 (96.7)		
Fatigue at admission	Present (n=5)	2 (40.0)	3 (60.0)	0.04	10.4 (1.5-70.4)
	Absent (n=149)	9 (6.0)	140 (94.0)		
Cough at admission	Present (n=29)	5 (17.2)	24 (82.8)	0.03	4.13 (1.16-14.65)
	Absent (n=125)	6 (4.8)	119 (95.2)		
Breathlessness at admission	Present (n=11)	3 (27.3)	8 (72.7)	0.03	6.3 (1.4-28.5)
	Absent (n=143)	8 (5.6)	135 (94.4)		
Fever at admission	Present (n=26)	2 (7.7)	24 (92.3)	1.0	1.1 (0.22-5.42)
	Absent (n=128)	9 (7.0)	119 (93.0)		
Headache at admission	Present (n=25)	1 (4.0)	24 (96.0)	1.0	0.50 (0.06-4.05)
	Absent (n=129)	10 (7.8)	119 (92.2)		
Rhinitis at admission	Present (n=23)	1 (4.3)	22 (95.7)	1.0	0.55 (0.07-4.51)
	Absent (n=131)	10 (7.6)	121 (92.4)		
Myalgia at admission	Present (n=13)	2 (15.4)	11 (84.6)	0.23	2.7 (0.51-13.9)
	Absent (n=141)	9 (6.4)	132 (93.6)		
Features	Category	Symptoms at 3 months		P	Odds ratio (95% CI)
		Present (n=18), n (%)	Absent (n=136), n (%)		
Gender	Male (n=57)	3 (5.3)	54 (94.7)	0.05	0.30 (0.08-1.09)
	Female (n=97)	15 (15.5)	82 (84.5)		
Hypertension	Present (n=7)	1 (14.3)	6 (85.7)	0.59	1.28 (0.14-11.24)
	Absent (n=147)	17 (11.6)	130 (88.4)		
COVID positive family member	Present (n=63)	10 (15.9)	53 (84.1)	0.18	1.96 (0.73-5.28)
	Absent (n=91)	8 (8.8)	83 (91.2)		
Cough at admission	Present (n=29)	3 (10.3)	26 (89.7)	1.0	0.85 (0.23-3.14)
	Absent (n=125)	15 (12.0)	110 (88.0)		
Breathlessness at admission	Present (n=11)	1 (9.1)	10 (90.9)	1.0	0.74 (0.90-6.16)
	Absent (n=143)	17 (11.9)	126 (88.1)		
Fever at admission	Present (n=26)	2 (7.7)	24 (92.3)	0.74	0.58 (0.13-2.70)
	Absent (n=128)	16 (12.5)	112 (87.5)		
Headache at admission	Present (n=25)	3 (12.0)	22 (88.0)	1.0	1.04 (0.28-3.89)
	Absent (n=129)	15 (11.6)	114 (88.4)		

Hypertension was the most frequent co-morbidity identified among the study participants. Presence of any co-morbidity was not found to be significantly associated with post COVID 19 events. A study conducted in Singapore could elicit that demographic and ethnic differences could bring a significant proportion of patients resulting in persistent symptoms rather than an acute severe infection.^[19] Family history of COVID 19 positive patient turned out to be a significantly associated with post COVID 19 events in this study. Because COVID 19 spreads from person to person, family members are potential sources of infection due to the risk of high viral load that they carry, a major challenge in the control of the disease.^[27] It could be due to clustering of cases within families residing in coastal belts, those with a high load of the virus could rapidly spread the disease due to the socioeconomic vulnerability prevailing in the coastal community. In a study done in Ecuador, it was found that virus spread was faster in lower altitudes due to demographic and cultural differences.^[28] In this study, symptoms like fatigue, cough and breathlessness at the time of acute COVID 19 infection were found to be risk factors

for developing post COVID events. Hence acute infection with COVID 19 can result in post COVID symptoms in these groups of patients and requires vigilance and follow up for timely pick up of patients before ending in complications.

As the morbidity burden is being shifted from COVID to post-COVID, primary care physicians must change their role from prevention and management of the infectious disease to that of its long-term sequelae. Knowledge regarding post COVID symptoms will help in the early diagnosis and treatment at the community level. Post COVID clinics at the primary health care level will help to reduce the excess strain that the health system may face during the pandemic. However, management of post COVID syndrome often demands a multidisciplinary approach and the family physicians have to seek expertise from psychologists, dietitians, physiotherapist and allied specialties. Hence equipping primary care physicians on this will help to strengthen the health care system and will help to avoid unnecessary referrals for the same.^[11,29] Further research is needed

on the rehabilitation of patients with post COVID symptoms to hasten the functional recovery and to improve the quality of life.^[21]

Conclusion

Post COVID syndrome is common among COVID 19 patients with minimal symptoms as well. But those patients showing fatigue, cough and breathlessness as symptoms during the early phase of their disease are more likely to develop post COVID syndrome. Fatigue, headache, myalgia, joint pain and exertional dyspnea are the predominant long-lasting symptoms detected in the current analysis.

Key message: Patients with minimal symptoms during acute COVID 19 are likely to get post COVID symptoms. In primary care, understanding long term consequences of COVID 19 is important as a significant amount of morbidity during and after the COVID-19 pandemic will be that of post-COVID symptoms.

Acknowledgements

We would like to extend thanks to the staff of the CFLTCs and the participants of the study None.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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