

Original Research Article

Incidence and probable risk factors of post COVID syndrome among COVID-19 patients in urban population of North Kerala: a 6 months cohort study

Deepa K. R.^{1*}, Bindu Mohandas¹, Jayakrishnan Thayyil¹,
Meera S. Nair¹, Rosh P.², Durgesh Kumar¹

¹Department of Community Medicine, ²Department of General Medicine, KMCT Medical College, Calicut, Kerala, India

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*Correspondence:

Dr. Deepa K. R.,

E-mail: deepa2013kkd@gmail.com

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ABSTRACT

Background: Post-COVID condition is an important health burden all over world. This study was conducted to determine incidence, symptoms and risk factors of post COVID syndrome.

Methods: Cohort study was done on COVID-19 patients of Mukkam Municipality tested from Mukkam Community Health Centre. Baseline data was collected using pre-tested semi-structured questionnaire by direct interview method after obtaining their consent. Subjects were followed up weekly for 6 months to know occurrence of post COVID syndrome, its course and outcome if any. Incidence and relative risk for age, gender, COVID-19 vaccination status, comorbidities and severity of COVID-19 illness were assessed for post COVID syndrome. Chi-square test was used for statistical association between severity of COVID-19 and occurrence of post COVID syndrome.

Results: Among 800 persons tested for COVID-19, 28.75% were tested positive. Incidence of post COVID syndrome among study subjects was 42.2%. Relative risk for post COVID was high among participants having age more than 60 years (RR-1.76), females (RR-1.07), with comorbidities like diabetes (RR-1.28), hypertension (RR-1.06) and cardiac illness (RR-1.05), unvaccinated status (RR-1.21) and in severe COVID-19 infection (1.20). There is a significant statistical association between occurrence of post COVID syndrome and degree of severity of COVID-19 disease ($p=0.0046$).

Conclusions: Post-COVID syndrome was found more often in older people who had severe COVID-19 illness, also incidence increases with severe COVID-19 illness.

Keywords: Incidence, Post-COVID conditions, SARS-CoV-2, Postacute COVID-19 syndrome, Long-haul COVID, Sequelae

INTRODUCTION

The first case of COVID-19 in India was detected in Kerala on January 27, 2020 and India have been severely affected by this viral illness.¹ During 2020, the first wave transmitted in India was due to Wuhan strain. Second wave started in India during midst of 2021, which was due to delta wave. Increased mortality was reported during second wave. Like other parts of the world, India also suffered from burden of

post COVID syndrome and Kerala started post-COVID clinics in all government hospitals- from primary health centres to medical college hospitals to tackle this condition.² Post COVID syndrome is an illness described among patients who have recovered from COVID-19 but still have ongoing symptoms or among those who continued to have symptoms for longer than normally expected.³ In September 2020, World Health Organization (WHO) Classification of Diseases 10 (ICD-10) and ICD-11 codes

for post-COVID condition, and in October 2021, clinical case definition of post-COVID-19 condition was announced following a Delphi consensus process as 'a condition occurring 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 Long COVID can happen to anyone who has had COVID-19 infection, even if the illness was mild, or they had no symptoms. People with long COVID report experiencing different combinations of the symptoms like fatigue, difficulty thinking or concentrating, headache, loss of smell or taste, dizziness on standing, heart palpitations, chest pain, difficulty breathing or shortness of breath, cough, joint or muscle pain, depression or anxiety, fever etc and these symptoms are getting worse after physical or mental activities.^{5,6} Post COVID syndrome is a major health issue globally. A national representative sample survey by the UK Office for National Statistics estimates that around 1 in 10 respondents who tested positive for COVID-19 exhibit symptoms for a period of 12 weeks or longer. Other studies in the USA and Switzerland indicate that around a third of people who tested positive for SARS-CoV-2 had not returned to their usual state of health when interviewed 3 to 6 weeks after diagnosis.⁷ Only few studies on post COVID were conducted in India and much details not available. Since it is a new disease, the natural history was not well known, the manifestations may vary geographically and ethnically in different population. There is an immediate need to address post COVID manifestations, and for that more research on post COVID syndrome are required. Awareness about long COVID and characterization of its manifestation are important for early detection. In addition, more research should be directed to identify risk factors, exact mechanisms leading to the development of long COVID syndrome and association of occurrence of post COVID syndrome with severity of COVID-19 disease in persons infected with COVID-19. Many studies conducted on post COVID were cross sectional in nature and temporality could not be explained. So, we conducted a cohort study to detect incidence and risk factors associated with occurrence of post COVID syndrome among COVID-19 patients in urban population of North Kerala.

METHODS

This community based prospective cohort study was conducted at Mulkam Municipality in Kozhikode district of Kerala, India. Mulkam is a major municipality town in Kozhikode located around 27 kilometers east of Calicut city and has a population of 40,670. The period of study was 1st August 2021 to 31st July 2022(1year).⁸ All persons in this area diagnosed as COVID-19 was reported to CHC Mulkam.

Sampling method, size and subject selection

Universal sampling method was employed and sample size was taken as 238. Study subjects were natives of Mulkam

Municipality tested positive at CHC Mulkam or reported to CHC Mulkam. Contact information of COVID-19 tested positives from 1 October to 31 December 2021 were collected prospectively from register kept at public health department of CHC Mulkam. From that list persons above 18 years of age were contacted over phone and those who gave verbal informed consent for participating in this study were enrolled. Migrants who were not permanent residents, persons who were unable to contact after trying three times over phone, unable to recollect data and lost to follow up were excluded from the study.

Procedure

A cohort study was conducted among COVID-19 patients at Mulkam Municipality. During the study period, subjects were enrolled consecutively for the first three months. Then they were prospectively followed up every week for a period of 6 months. First the details of the positive subjects were collected from COVID 19 register kept at public health department of CHC Mulkam. Then they were contacted over phone and data regarding name, age and address were confirmed. As per the guidelines of Directorate of Health Services of Kerala government, the COVID positive subject needs to undergo 17 days of home or institutional isolation. Hence the direct interview was scheduled after 17 days of their test date.⁹

During direct interview on the first visit, after obtaining the written informed consent of the study subject, baseline data was collected using pretested semi structured questionnaire that consisted of sociodemographic data including age, gender, presence of comorbidities like diabetes, hypertension, cardiac illnesses; data on symptoms like fever, cough, fatigue etc and grade of COVID-19 illness according to the severity classification. After the first visit, the study subjects were followed up weekly for 6 months over phone to know the persistence or occurrence of post COVID syndrome if any and symptoms of post COVID like fatigue, cough, dyspnoea, palpitation, headache etc.

Those who had post COVID symptoms were further assessed in detail. Fatigue was assessed using Chalder fatigue score, memory using Mini- Mental Status Examination, depression was assessed using Patient Health Questionnaire-9 and dyspnoea using MRC Dyspnoea scale.¹⁰⁻¹³ The subjects were enrolled for study after obtaining verbal informed consent over phone. Latter during house visit, written informed consent was obtained from participants. Confidentiality of the data was assured to them at all the stages of the study.

Statistical analysis

Data was entered in Microsoft EXCEL and analysed by Statistical Package for Social Sciences (SPSS) software version 25. Results were expressed in number, mean±SD, percentage. The incidence rates were calculated and expressed as percentage. Relative risk with 95% confidence interval of variables like gender, age comorbidities,

vaccination status etc for post COVID syndrome was analyzed using MedCalc statistical software. Chi-square test was used to find out the association between post COVID Syndrome and severity of COVID-19 disease.

RESULTS

A total of 800 persons were tested for COVID-19 from Mukkam municipality area and reported to community health centre, out of which 238 were tested positive for COVID-19. The test positive rate was 29.75%. Among 238 COVID-19 positive study participants, one died due to respiratory failure and 2 were unable to contact. During follow up, 5 were lost to follow up. Finally, 230 (96.6%) COVID-19 patients were analysed in this study. The details of enrolment of the study participants are shown in the flow diagram below (Figure 1).

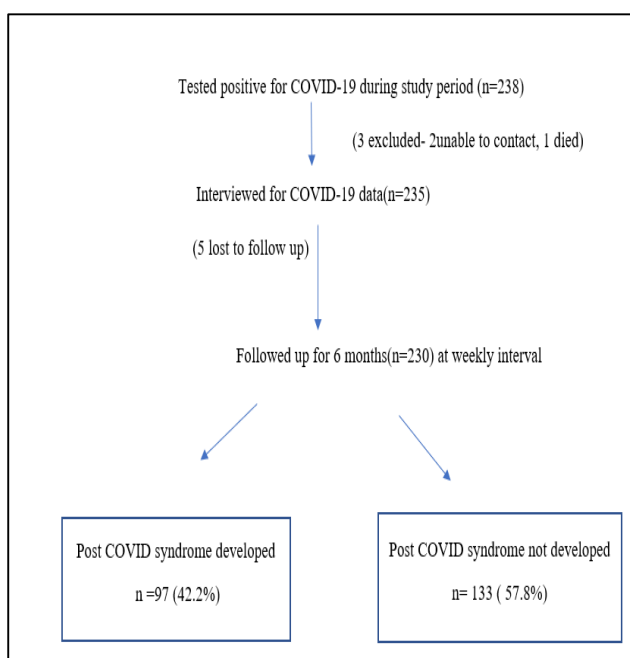


Figure 1: Flow diagram showing details of enrolment of the study participants.

COVID-19 test: Among the 230 study participants, 172 (74.8%) participants confirmed COVID-19 infection by doing COVID-19 antigen test and others 58 (25.2%) confirmed by RTPCR from government approved labs. Most common symptom of COVID-19 illness was fever (67.4%) followed by fatigue (33.5%) and cough (30.9%). Most common post COVID symptoms were fatigue (57.7%) followed by cough (45%), myalgia (34%), hair loss (32.9%) and dyspnoea (26.8%). Other manifestations reported were palpitation (13.4%), chest pain (3.09%) headache (8.25), hypersomnia (1.03%), nightmare (1.03%) etc. (Table 1).

Incidence of post COVID syndrome among participants was 42.2%.

Table 1: Symptomatology of COVID-19 disease and post-COVID syndrome.

Symptoms	COVID-19	Post COVID
	Frequency (%) (N=230)	Frequency (%) (N=97)
Fever	155 (67.4)	0
Fatigue	77 (33.5)	56 (57.7)
Cough	71 (30.9)	44 (45)
Loose stool	29 (12.6)	0
Sore throat	28 (12.2)	0
Myalgia	9 (6.5)	34 (35.05)
Dyspnoea	12 (5.2)	26 (26.8)
Palpitation	1 (0.43)	13 (13.4)
Chest pain	1 (0.43)	3 (3.09)
Headache	7 (3.04)	8 (8.2)
Hair loss	0	32 (32.9)

Gender

Among the participants, 125(54%) were males and 105 (46%) females. Incidence of post COVID among males was 40.8% and females it was 43.8%. Relative risk of developing post COVID for female gender was 1.07, (95% CI 0.79-1.45, p=0.64).

Age

Mean age of study participants was 34.63+18.7years. 12.2% of the participants were above 60 years of age. Among this, 67.85% developed post COVID. Relative risk was 1.76 and significant (95% CI-1.29-2.39, p=0.0003). Mean age of post covid was 43.4+14.1 years.

Comorbidities

Comorbidities were present in 20.4% of study population. Incidence of post COVID among them was 44.7%. Relative risk of developing post COVID among participants with comorbidities was 1.07 (CI-0.749-1.54, p=0.691). Diabetes: 7.4% of the study participants were diabetic. Incidence and relative risk were 52.9% and 1.28 (CI-0.796-2.062, p=0.30721) respectively. Hypertension: 7.8% of participants were hypertensive. Incidence of post COVID among hypertensives was 44.4% with a relative risk of 1.06 (CI-0.62-1.82, p=0.836). Cardiac illness: Among study participants, 3.4% had cardiac illness. Incidence of post COVID was 44.4% with relative risk of 1.05 (CI-0.5006-2.23, p=0.886).

Vaccination status

19.6% were unvaccinated. Incidence of post COVID among unvaccinated was 48.9% with relative risk of 1.2.

Severity of clinical illness

According to staging based on Severity of clinical illness, 87.3% developed moderate or severe illness. Incidence of

post COVID among them was 43.1% with relative risk of 1.2059 (CI=0.72-2.03, p=0.48) (Table 2). There is significant risk of getting post COVID syndrome among

severe COVID-19 cases compared to asymptomatic and mild cases (p=0.0048) (Table 3).

Table 2: Incidence and measurement of risk factors of post COVID syndrome

Variable	Frequency among study subjects (N=230)	Incidence of post COVID (N=97)	Relative risk	95% CI	P value
Gender					
Male	125 (54)	51 (40.8)	1.07	0.79-1.45	0.6400
Female	105 (46)	46 (43.8)			
Age (years)					
<60	202 (87.8)	78 (38.61)	1.76	1.29-2.39	0.0003
>60	28 (12.2)	19 (67.85)			
Co morbidities					
Present	47 (20.4)	21 (44.7)	1.07	0.749-1.54	0.6910
Absent	183 (79.6)	76 (41.5)			
Diabetes					
Present	17 (7.4)	9 (52.9)	1.28	0.79-2.06	0.3071
Absent	213 (92.6)	88 (96.9)			
Hypertension					
Present	18 (7.8)	8 (44.4)	1.06	0.61-1.81	0.8361
Absent	212 (92.2)	89 (96.9)			
Cardiac illness					
Present	9 (3.9)	4 (44.4)	1.05	0.50-2.23	0.8860
Absent	221 (96.1)	93 (95.9)			
Vaccination					
Not vaccinated	45 (19.6)	22 (48.9)	1.21	0.85-1.70	0.2888
Vaccinated	85 (80.4)	75 (40.6)			
Severity of clinical illness					
Asymptomatic and mild	28 (12.7)	18 (64.3)	1.21	0.72-2.03	0.4817
Moderate and severe	202 (87)	87 (43.1)			

Table 3: Association of COVID-19 disease and occurrence of post COVID syndrome.

Severity	Post-COVID manifestations		Total	Chi square test	P value
	Present	Absent			
Asymptomatic & mild	10 (35.7)	18 (64.3)	28 (12.2)	10.75	0.0046
Moderate	49 (35.5)	89 (64.5)	138 (60)		
Severe/Critical	38 (59.4)	26 (40.6)	64 (27.8)		
Total	97	133	230		

DISCUSSION

A cohort study was conducted in Mukkam Municipality among COVID-19 patients. Since the COVID-19 patients were asked to keep in isolation either at home or institution for 17 days, the participants were direct interviewed after this period. We assessed incidence and symptoms of post COVID-19. Also assessed the risk of probable risk factors like age, comorbidity, severity of infection, vaccination status etc for developing post COVID syndrome.

In a study on defining post COVID syndrome suggested that determining the prevalence of post-COVID symptoms should be based on the presence of temporal relationship between the symptoms and COVID-19; and appearance of symptoms after the SARS-CoV-2 infection (new post-COVID symptoms, not being previously present).¹⁴ So we conducted a cohort study to know the temporality and also to confirm the findings of the currently available cross sectional studies. Incidence of post COVID syndrome: Incidence of post COVID syndrome in our study was 42.2%. In two studies, one conducted at Egypt and another clinical review it was 10-15%.^{15,16} Another study conducted

in Greece found that incidence of post-COVID syndrome among general population was around 10-35% and for hospitalized patients it may reach 85%.¹⁷ Symptoms and severity of COVID-19 disease: In our study, 12.2% constitutes asymptomatic and mild COVID-19 patients. 60% of study participants had moderate symptoms and 27.8% developed critical illness. It was also found that risk of getting post COVID was higher among participants who had moderate to severe illness compared to those with mild illness or without symptoms (RR-1.2, CI= 0.72 to 2.03 p=0.4817), but not significant which may be attributed to lower sample size. It was also found that risk of getting post COVID syndrome was higher among severe COVID-19 cases compared to asymptomatic and mild cases and statistically significant also. It was similarly reported in other international studies too.¹⁶ In our study fever (82%), fatigue (40.7%) and cough (37.5%) were commonly encountered symptoms in the study subjects. In a multicentre observational study conducted using the data from the NCRC, predominant symptoms were fever (71.7%), shortness of breath (48.6%), dry cough (39.8%) and fatigue (12.3%) during the second wave.²¹ Our study was also conducted during the second wave in India.

Gender

COVID-19 incidence does not vary greatly between sexes. In our study, the proportion of female gender developed post COVID was slightly higher than males. It was similarly reported in other studies conducted all over the world.^{15,19-21} Studies suggest that while men tend to suffer most acute symptoms of COVID-19, continued inflammatory reaction leads to a higher likelihood of having long COVID among females.²² The biological plausibility is yet to explore.

Age

In our study, mean age of participants was 34.63±18.7 years. People of all age group are at risk of getting post COVID syndrome, but risk of getting post COVID was higher among people more than 60 years of age compared to youngsters (RR-1.76, CI- 10.29 to 2.39. p=0.0003). This was similarly reported from other international studies also.²³ Another study conducted in a tertiary care center in the same part of South India, found that majority of COVID-19 deaths happened in the age group more than 60 years.²⁴

Comorbidities

In our study people with comorbidities like diabetes, hypertension, chronic kidney diseases, cancers are having higher risk of post COVID syndrome compared to others without comorbidities. Relative risk of post COVID among persons with diabetes, hypertension and cardiac illness were higher but not statistically significant. It may be due to small sample size. Among the comorbidities, diabetes was having higher risk (RR-1.28). Same finding was obtained in other studies conducted in USA.^{21,25} Our

COVID-19 management strategies including COVID-19 vaccination strategy gave more focus on persons with comorbidities and older age group. 'Reverse quarantine' was also beneficial.

Vaccination status

Unvaccinated people are at higher risk of developing post COVID when compared to vaccinated. This was similarly reported in a US study.²⁶ In a systematic review also, after taking vaccination showed some improvement for long COVID symptoms.²⁷ Post COVID syndrome manifestations: According to WHO, more than 200 varieties of symptoms have been reported which have an impact on every day functioning for post COVID; the most common symptoms were fatigue, shortness of breath and cognitive dysfunction.²⁸

Fatigue (57.7%) was the most common symptom of post COVID syndrome in our study. In a study conducted among patients attended district post-COVID clinic, Wayanad (October 2020 to June 2021), 32.2% developed fatigue.²⁹ Another studies conducted in Egypt and Oman also, the most common symptom encountered was fatigue (72.8 %).^{16,30} In a meta-analysis study, overall prevalence of fatigue was 23%.³¹ A clinical review found hypometabolism in the frontal lobe and cerebellum in COVID-19 patients with fatigue and is likely caused by systemic inflammation and cell-mediated immune mechanisms. Negative psychological and social factors associated with the COVID-19 pandemic have also been linked to chronic fatigue.³²

Other symptoms

Cough: In our study predominant symptom next to fatigue was cough. In the Wayanad district post-COVID clinic study also reported cough (25.6%).²⁹ Persistent cough in post-COVID syndrome was suggested because of neuroinflammation leading to a state of laryngeal and cough hypersensitivity, which is the basis for chronic refractory or unexplained cough.³³ Myalgia was present among 35.05% participants with post COVID in our study. Possible mechanism for post COVID myalgia was presence of Angiotensin Converting Enzyme 2 positive cells in the human spinal cord, causing the reduction of ACE-2 and Angiotensin (1-7). This reduction of Angiotensin (1-7) can increase p38 MAPK phosphorylation, which results in hyperalgesia.³⁴ Dyspnoea was present among 26.8% of participants with post COVID syndrome in our study. It was higher (48.3%) in the study done at Wayanad, this may be due to the factor that it was conducted in patients of post COVID clinic.²⁹ Dyspnoea in post COVID syndrome is attributed to underlying viral and immune mediated implications.³⁵ Palpitation: In our study, 13.4% developed palpitation. Another studies attributed most of the palpitations in post COVID syndrome due to postural orthostatic tachycardia syndrome (POTS) or nervous dysregulation or some other causes.^{36,37} Headache: 8.2% of participants with post COVID developed headache.

Another study suggested that patients with prior history of headache also reported a worsening of headache.³⁸ Hairloss was present among 32.9% of the participants with post COVID in our study. Hair loss was explained as a condition known as Telogen effluvium. COVID-19 induced stress resulted in Telogen effluvium.³ Though fever was the most common symptom among COVID 19 patients because of viremia, fever was not manifested as a post COVID symptom in our study.

Strengths and limitations

All the persons who are natives in this area and diagnosed from any labs or hospital as COVID-19 was reported at CHC Mukkam. Their data was available and retrieved from the records. We were able to do maximum follow up of the COVID-19 patients (96.6%). Also this study was conducted during August to October, 2021 while Delta was the predominant strain circulating with increased morbidity and mortality reported all over the country. Also post COVID syndrome started as a major health issue this time. The observational study was conducted in cohort design for a follow up period of 6 months with weekly contact. So the incidence rate calculation and temporality were explained better. Study was conducted during the second wave of COVID-19 pandemic. During the peak of second wave, COVID-19 restrictions were made strict including social distancing measures, quarantine, lock down etc. So we faced difficulties in conducting direct interviews. We were also unable to do direct physical examination of the participants.

CONCLUSION

Incidence of post COVID was 42.2% in our study. It was higher among older people and in persons who had severe COVID-19 illness. Female gender is also a risk factor for post COVID. Most common manifestation of post COVID syndrome is fatigue. Early detection, proper monitoring and treatment is needed especially in severe COVID-19 patients to reduce occurrence and severity of post COVID manifestations.

Recommendations

This study was done in a local area with small sample size. Another multi centred cohort study with large sample size to be conducted for generating information, extrapolating or generalizing this information.

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