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Original Research Article

Beyond recovery: post COVID-19 complications

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ABSTRACT

Background: Although most patients recover from the acute phase of coronavirus disease 2019 (COVID-19), a substantial proportion continue to experience persistent symptoms and organ-specific complications, collectively referred to as post COVID-19 syndrome (PCS). These manifestations like pulmonary fibrosis emerging as a significant long-term concern, particularly among those with moderate to severe illness. Data on the prevalence, spectrum, and risk factors of post-COVID complications from the Indian subcontinent remain limited.
Methods: A prospective study was conducted at the department of pulmonary medicine, Mediciti Institute of Medical Sciences, involving 100 patients who recovered from acute COVID-19. Data collection included assessments at 1, 3, and 6 months post-recovery, using the WHO Global COVID-19 Clinical Platform Case Report Form. HRCT chest scans and relevant investigations were performed, with statistical analysis conducted using SPSS version 26.
Results: 68% of participants developed PCS, with higher incidence among older patients (>60 years, 57.3%) and females (44.1%). Complications observed were pulmonary fibrosis (26.4%), deep vein thrombosis/pulmonary thromboembolism (2.9%), heart failure (2.9%), tuberculosis (1.4%), and pneumothorax (1.4%). Significant associations were found between PCS and factors such as age, sex, smoking, severity of COVID-19, admission status, and vaccination status ($p<0.05$).
Conclusions: PCS is prevalent among recovered COVID-19 patients, especially older adults, females, smokers, and those with severe illness. Vaccination appears to have a protective role. Long-term follow-up and comprehensive rehabilitation programs are essential for managing PCS, particularly for high-risk groups.

Keywords: Age, Post COVID fibrosis, Smoking, Vaccination

INTRODUCTION

The highly contagious virus known as COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the highly contagious illness that has devastated the world's demographics that have caused over 6 million fatalities globally, making it the greatest health calamity to affect the planet since the 1918 influenza pandemic.[1]

Soon after Wuhan, Hubei Province, China, reported the first cases of this mostly respiratory viral illness in late December 2019, the pathogen causing these unusual infections was identified to be a new coronavirus that belonged to the Corona viridae family; it was given the name SARSCoV-2, or severe acute respiratory syndrome coronavirus. It was shown to have a significant degree of homology with the SARS coronavirus (SARS-CoV), which caused the respiratory pandemic in 2002-2003.[2]

Due to the quick global spread of SARS-CoV-2, the World Health Organization (WHO) had to designate the virus a global pandemic on March 11, 2020. While significant advancements in clinical research have improved our understanding of SARS-CoV-2 and COVID-19 management, it is becoming more and more important to stop the spread of this virus and its variations. SARS-CoV-2, the virus that causes COVID-19, has spread to 223

countries since the WHO proclaimed it to be a global pandemic, with over 593 million cases and over 6 million fatalities recorded worldwide.

The WHO now estimates that 2.2% of COVID-19 cases worldwide result in death. However, there are large national variations in the case fatality rate, which is influenced by age, underlying medical illnesses, and the severity of the illness.[1] About 5% to 8% of infected patients experience hypoxia, bilateral lung infiltrates, or mild to moderate disease, despite the fact that the majority of COVID-19 patients are asymptomatic or have mild to severe disease reduced compliance of the lungs necessitating mechanical ventilator support or non-invasive ventilation (NIV).

The primary approach to treating COVID-19 infection is supportive. While numerous treatments, including antiviral medications, monoclonal antibodies, anti-inflammatory medications, and immunomodulatory for the treatment of COVID-19, medicines were made available under emergency use authorization (EUA); the effectiveness of these therapies varies depending on the course and severity of the illness as well as specific risk factors.[3]

The individuals who recovered from the previous SARS-CoV and MERS-CoV epidemics had severe fatigue, a lowered quality of life (QOL), persistent dyspnea, and behavioral health issues. These individuals placed a significant burden on the local healthcare systems in the areas where the epidemics occurred.[3]

Similarly, in a small percentage of cases, a collection of different clinical symptoms known as post-acute COVID-19 syndrome has been reported in patients who recovered from SARS-CoV-2 induced COVID-193 despite biochemical evidence showing that SARS-CoV-2 replication stops four weeks after the initial infection (based on viral isolates sampled from the respiratory tract rather than the nasopharyngeal/oropharyngeal specimen).

METHODS

Study design and setting

It was a prospective study conducted at the department of pulmonary medicine, Mediciti Institute of Medical Sciences, Medchal.

Study duration

This study was done for the period of 12 months (January 2021 to December 2021).

Sample size and study population

Total 100 patients attending OPD/admitted at MIMS was enrolled in the study.

Inclusion criteria

Age more than 18 years, RTPCR confirmed acute COVID-19 illness, RTPCR negative at time of discharge.

Exclusion criteria

Age less than 18 years, suspected acute COVID-19 illness not confirmed by RTPCR, RTPCR positive at time of discharge, active fever, active pulmonary tuberculosis, preexisting heart conditions like coronary artery disease, rheumatic heart disease, etc., chronic lung conditions like asthma, COPD, interstitial lung disease, etc.

Study procedure

After obtaining oral and written informed consent, recovered patients of COVID-19 of age more than 18 years, who had a positive RT PCR report at least 2 weeks prior, were enrolled in the study

Recovery from acute COVID-19 infection was considered when: i) the patient had no fever for three consecutive days, or improved in COVID-19 related symptoms (or) ii) discharged in case of hospitalization, without requirement of oxygen support (or) iii) two subsequent negative RT-PCR results for SARS-CoV-2, 24 hours apart.

The severity of acute COVID-19 was defined as mild, moderate or severe with reference to national guidelines for COVID-19: i) mild- patients with COVID-19 without evidence of breathlessness or hypoxia (defined as room air oxygen saturation ≤94%); ii) moderate- patients who had breathlessness and a room air oxygen saturation (SpO_2) of ≥90% and ≤93%; and iii) severe- patients with room air SpO_2 of <90%.

Patients were assessed and evaluated at 1 month, 3 months, and 6 months after recovery and following investigations (those applicable) were done- CBP, chest x-ray PA, HRCT chest, ECG,2D ECHO, spirometry and HRCT chest scan was performed at 3 month interval in patients with moderate and severe COVID-19.

Pulmonary fibrosis was described as either severe fibrosis based on the presence of traction bronchiectasis and honeycombing or mild/moderate fibrosis if it was limited to parenchymal bands and interlobar septal thickening. Patients with pulmonary fibrosis underwent a second CT scan at 6 months to monitor changes and further investigations in view of complaints were done.

Statistical analysis

The data collected were entered into Microsoft excel 360 in order to create a master chart. The master chart was then loaded into statistical package for social sciences (SPSS) version 26 for further statistical analysis. Both quantitative and qualitative variables were present in the master chart.

Both descriptive and inferential statistics were used for analysis

For describing the qualitative variables, frequency and percentages were used. For describing the quantitative data, mean and standard deviation were used. To find out the distribution of qualitative variable among those with PCS and not, Chi square test was applied. A p value of less than 0.05 was considered to be statistical significance.

Ethical issues

Institutional ethics committee approval was obtained.

RESULTS

Males constituted a higher proportion of the study population (63%) compared to females (37%). Participants aged >60 years formed the largest age group (45%). A higher proportion of females were aged >60 years (54.1%) compared to males (39.6%).

Table 1: Age and sex wise distribution of participants.

Age group (in years)	Male		Female		Total	
	N	%	N	%	N	%
<40	17	26.9	6	16.2	23	23
40-60	21	33.3	11	29.7	32	32
>60	25	39.6	20	54.1	45	45
Total	63	63	37	37	100	100

Middle-aged participants (40-60 years) accounted for nearly one-third (32%) of the study population. Younger participants (<40 years) constituted the smallest age group (23%), with male predominance.

Table 2: Distribution according to the presence of Post COVID-19 syndrome.

Post COVID-19 syndrome	Frequency (n=100)	Percentage
Present	68	68
Absent	32	32

Post COVID-19 syndrome (PCS) was present in 68% of the study participants. Nearly one-third of patients (32%) did not report persistent symptoms after recovery. The high prevalence of PCS highlights a substantial burden of long-term morbidity following acute COVID-19 infection. These findings underscore the need for systematic post-recovery follow-up in COVID-19 survivors.

Among various post COVID-19 symptoms, most common was fatigue and its median duration was around 65 days, least common was disturbance in sleep. Arthralgia was present for about longer duration.

Table 3: Distribution of post COVID-19 symptoms among the participants along with median duration of symptoms.

Poat COVID symptoms	Frequency (n=100)	Median duration of symptoms in days
Cough	29	45 (12-85)
Dyspnea	27	37 (18-62)
Chest pain	21	38 (21-48)
Fatigue	52	65 (43-184)
Headache	10	41 (15-65)
Anosmia	6	27 (12-35)
Dysgeusia	7	24 (12-38)
Sleep disturbance	5	40 (28-63)
Myalgia	18	57 (42-128)
Arthralgia	12	69 (35-182)

Most common complication in post COVID-19 patients found to be pulmonary fibrosis, which was seen in 26.4% of post COVID-19 patients.

Table 4: Distribution of complications among Post COVID-19 patients.

Complications	Frequency (n=68) (%)
Pulmonary fibrosis	18 (26.4)
Pneumothorax	1 (1.4)
DVT/pulmonary thromboembolism	2 (2.9)
Tuberculosis	1 (1.4)
Heart failure	2 (2.9)

Among the participants with PCS, 57.3% were aged more than 60 years and among the participants without PCS it was 18.7%. Age more than 60 years was found to be associated with PCS with p value of less than 0.05.

Table 5: Association between age and development of post COVID syndrome.

Age group (in years)	PCS				χ^2	P value
	Present (n=68)		Absent (n=32)			
	N	%	N	%		
<40	4	5.8	19	59.3	35.78	0.001
40-60	25	36.7	7	21.8		
>60	39	57.3	6	18.7		

Table 6: Association between sex and development of PCS.

Sex	PCS				χ^2	P value
	Present (n=68)		Absent (n=32)			
	N	%	N	%		
Male	38	55.8	25	78.1	4.61	0.031
Female	30	44.1	7	21.8		

Among the participants with PCS, 55.8% were males and among the participants with no PCS, 78.1% were males. Females were more prone to PCS than males with p value of less than 0.05.

Table 7: Association between smoking and development of PCS.

Smoker	PCS				χ^2	P value
	Present (n=68)		Absent (n=32)			
	N	%	N	%		
Yes	21	30.8	2	6.3	7.45	0.006
No	47	69.1	30	93.7		

Smokers had a significantly higher prevalence of post COVID-19 syndrome (PCS) compared to non-smokers. Among patients with PCS, 30.8% were smokers, whereas only 6.3% of patients without PCS had a history of smoking. The majority of patients without PCS were non-smokers (93.7%). Smoking status showed a statistically significant association with the development of PCS (χ^2=7.45; p=0.006).

Table 8: Association between severity of acute covid illness and development of PCS.

Severity of COVID	PCS				χ^2	P value
	Present (n=68)		Absent (n=32)			
	N	%	N	%		
Mild	24	35.2	26	81.3	20.24	0.001
Moderate	26	38.2	6	18.7		
Severe	18	26.4	0	0		

The prevalence of post COVID-19 syndrome (PCS) increased with increasing severity of acute COVID-19 illness. All patients with severe COVID-19 illness (100%) developed PCS, with none remaining asymptomatic post-recovery. Among patients with moderate illness, 38.2% developed PCS, while 18.7% did not. Patients with mild COVID-19 illness had a comparatively lower burden of PCS, with 35.2% developing persistent symptoms. Severity of acute COVID-19 illness showed a strong and statistically significant association with PCS (χ^2=20.24; p=0.001).

Table 9: Association between admission risk and development of PCS.

Admitted for COVID	PCS				χ^2	P value
	Present (n=68)		Absent (n=32)			
	N	%	N	%		
Yes	46	67.6	4	12.5	26.47	0.002
No	22	32.3	28	87.5		

A significantly higher proportion of patients who were hospitalized for acute COVID-19 developed post COVID-19 syndrome (67.6%) compared to those who were not admitted (32.3%). Among patients without PCS, the majority (87.5%) had not required hospitalization during the acute illness. Hospital admission for COVID-19 showed a strong and statistically significant association with the development of PCS (χ^2=26.47; p=0.002).

Table 10: Association between vaccination status and PCS.

Vaccine received	PCS				χ^2	P value
	Present (n=68)		Absent (n=32)			
	N	%	N	%		
Yes	40	58.8	28	87.5	8.22	0.004
No	28	41.2	4	12.5		

Among those with PCS, 41.2% were not vaccinated and among those without PCS, 12.5% were not vaccinated. The development of PCS was more among the participants who were not vaccinated than the participants who were vaccinated with p value of less than 0.05.

DISCUSSION

The COVID-19 epidemic has impacted several hundred million individuals. It has been shown that some symptoms persist even after healing. The quality of life for patients is greatly impacted by these post COVID-19 effects. An increasing number of patients are exhibiting long COVID, or post COVID-19 consequences presenting a cluster of symptoms, extrapulmonary and pulmonary, with understood or unknown causes.[4]

While comparing results from studies with varying follow-ups (15 days to 7 months) and populations might be difficult, the overall incidence of post COVID-19 syndrome has been reported to range between 35% and 94%. In our study, 68% of patients had either long COVID or post COVID-19 syndrome.

Of the 100 patients in our cohort, 50 patients (or 50%) had mild sickness, 32 patients (or 32%) had moderate illness, and 18 patients (or 18%) had severe disease. Compared to earlier research, ours contained a higher proportion of mild and asymptomatic patients recruited; several of the included studies had a danger of selection bias, with symptomatic patients more likely to seek medical attention.

45 participants (45%) were in the age group >60 years, followed by 32 (32%) in the age group 40 to 60 years, and 33 (33%) in the age group <40 years of age. 63 participants (63%) were male and 37 (37%) were females. 68 participants (68%) had received at least one dose of vaccination at the time of study.

All moderate and severe patients (n=50;50%)) had been admitted in the hospital during their acute illness.

All patients suffering from severe COVID-19 infection received both oxygen and NIV. Among those suffering from moderate COVID-19, all received oxygen and 15.6% received NIV.

55 (55%) participants had received steroids. All the participants who had severe and moderate COVID-19 illness (n=50; 50%) had received steroids and 5 participants (10%) of mild disease also did so

Among those admitted, the average length of stay was 8.43±2.82 days.

Myalgias and exhaustion are two chronic musculoskeletal issues that have been documented in 37-62% of COVID-19 patients who have recovered.

In our sample, fatigue accounted for 52% of post COVID-19 symptoms, while myalgia was reported in 18% of cases. Research has shown that individuals with post COVID-19 tiredness exhibit hypometabolism in the frontal and cerebellar regions.[4]

Reductions in neurotransmitter levels, suppression of motor neuron unit firing, inflammation, and decreased neuronal excitability have all been proposed as major causes of post COVID-19 tiredness.[5] Anemia, hypothyroidism, vitamin D insufficiency, and underlying chronic disorders are examples of metabolic variables that can cause prolonged fatigue and myalgia.

Apart from fatigue, many patients suffered from prolonged respiratory complaints, including cough (29%) and shortness of breath (27%) and chest pain (21%).

Acute COVID-19 is characterized by pulmonary parenchymal damage and acute respiratory distress syndrome (ARDS). Direct viral damage, cytokine- and cell-mediated harm, profibrotic pathway activation, and trauma brought on by encouragement Lung parenchyma may become permanently scarred as a result of ventilation.[6] Furthermore, the pulmonary vasculature sustains significant damage as a result of COVID-19-induced thromboembolic microangiopathy and the immune-inflammatory cascade that follows.[7] This could account for the elevated incidence of chest discomfort in dyspnea patients after COVID-19.

Cough hypersensitivity leading to persistent cough in post COVID-19 patients has been linked to neurotropism by the SARS-CoV-2 virus, neuronal inflammation mediated by direct invasion and bystander harm by the immunological response to the virus, and neuroimmunomodulation through the vagus nerve.[8]

In our study, 5% of the patients had sleep difficulties. Prior research involving previous SARS-CoV infections suggested that the hypothalamus may be involved in these symptoms. The infection enters the hypothalamus by the olfactory pathway and disrupts the lymphatic drainage of the hypothalamus, causing the hypothalamus to produce proinflammatory cytokines, interleukins, and interferon gamma, which results in such symptoms.

Similar to a study conducted by Penghin et, incidence of anosmia (6%) and dysgeusia (7%) was observed more frequently in patients with mild and moderate illness.[9]

Spirometry revealed obstructive airway disease in 12.5% of moderate and 6% of mild COVID-19 cases. There are two possible explanations for this. First, a previously unidentified airway condition could be the cause illnesses among the patients. The second explanation can be COVID-19 illness, which causes anomalies in the bronchi. Necrotising bronchiolitis and focal bronchial or bronchiolar inflammation were discovered during the autopsy of deceased COVID-19 individuals, which may account for the obstructive lung abnormalities. In a study by Eskombatchai et al, lung fibrosis was found in 85.7% of the patients with severe pneumonia on chest radiographs, and those patients also had poor lung function.[10] Similarly, in our study, pulmonary fibrosis was observed in 4 individuals (2.5%) with mild COVID-19 and 14 participants (77.7%) with severe COVID-19 and all had restrictive lung function.

As a result, individuals who have recovered from severe pneumonia should have regular follow-up to check on their pulmonary function, chest radiographs, and symptoms. They may also benefit from further pulmonary rehabilitation.

Within the three- and six-month follow-up periods, we examined the emergence of lung fibrotic alterations in 50 patients who had recovered from moderate to severe COVID-19 pneumonia. During the three-month follow-up, 18 (36%) of the subjects had evidence of fibrotic abnormalities, with 2 of them having severe fibrosis. Additionally, we discovered that, of the 18 patients who had a second chest CT scan at six months' follow-up, eight had basically unchanged lung fibrosis, while ten had somewhat decreased it.

In the study by Han et al, fibrotic abnormalities were seen in 35% of the patients over the 6 months of follow-up, which was in accordance with the results obtained in our study.[11] Also, other study by Ali et al showed a rate of 32% for pulmonary fibrosis in the COVID-19 patients within 3-month follow-up, which was lower than what we found in this study.[12] These variations could be explained by differences in studies population and paraclinical measures and management by technicians and clinicians.

Although the primary cause of post COVID-19 pulmonary fibrosis is still unknown, several studies suggest that aberrant immune systems and the ensuing cytokine storm may be involved.[13] Furthermore, further research must be done to elucidate the reasons why some patients experience lung fibrosis and others do not. According to a study by Han et al, our research indicated that severity may

be a risk factor in the development of pulmonary fibrosis.[11] It should be noted that opinions on the use of anti-fibrotic medications in the prevention and treatment of COVID-19 survivors' lung fibrosis are still divided. These medications are now utilized to treat interstitial lung disorders and have the ability to reduce pulmonary damage in high-risk patients.[14]

Other complications like deep vein thrombosis with pulmonary thromboembolism (2.9%), heart failure (2.9%), tuberculosis (1.4%) and pneumothorax (1.4%) were encountered among the patients with post COVID condition in our study.

Study by Mahmud et al identified female sex, moderate or severe illness during acute infection as risk factors for development of Post COVID-19 symptoms.[15]

Age was found to have a substantial impact on the development of PCS, as evidenced by the greater impact that PCS had on those over 60. Women were more likely than men to develop PCS comparable to past research. The incidence of PCS was significantly influenced by the severity of the acute COVID disease, hospitalization, and hypoxia needing either oxygen support or non-invasive ventilation. Patients who required admission and oxygen support, and who were deemed moderate to severely unwell, were more susceptible to developing PCS.

Vaccinated patients had reduced incidence of post COVID-19 symptoms, according to several investigations.[16,17] The development of PCS was more common in our study's non-vaccinated subjects than in the vaccinated ones, suggesting that vaccines may have a preventive effect.

The study has few limitations. It was performed in a single centre, introducing a potential selection bias. Baseline data on pulmonary function was unavailable. The study population was also small, and a larger population and longer follow up studies are necessary to understand the full spectrum of health consequences from COVID-19.

Primary care doctors now need to focus on managing the long-term effects of the infectious disease rather than just preventing it, as the morbidity load is shifting from COVID to post-COVID.

Understanding post-COVID symptoms will facilitate early community diagnosis and treatment. Primary care post-COVID clinics will lessen any additional burden that the health system might experience during the epidemic. The treatment of post-COVID syndrome frequently necessitates an interdisciplinary approach. Therefore, providing primary care physicians with this knowledge will help to improve the healthcare system and reduce the number of needless referrals for the same. To speed up the functional recovery of individuals with post-COVID symptoms and to improve the quality of life more research is required.

CONCLUSION

Patients with COVID-19 require long-term follow-up even after recovery for observation and management of their post-COVID ailments. A comprehensive rehabilitation program is essential for such patients during hospitalization and after their discharge. Older age group, female patients, those with severe illness requiring hospitalization and oxygen support/ non-invasive ventilation, and non-vaccinated were more prone to PCS, and require special attention in their post COVID state.

Also, patients with severe COVID-19 pneumonia were at a higher risk of pulmonary fibrosis. In addition, some patients experienced diminished fibrotic abnormalities in their chest CT on 6-month follow-up, while some others did not. Identifying and controlling these predictive factors, as well as evaluating the therapeutic position of the anti-fibrotic drugs, in clinical practice can help in preventing the development of and/or reducing the progression of the lung fibrosis.

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