Predictors of post COVID complications in patients admitted with moderate to severe COVID symptoms: A single center, prospective, observational study

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Abstract

While the world was still busy battling active COVID-19 infections, a large subset of patients started showing prolonged symptoms or developing complications following an initial recovery from COVID-19. Post-COVID complications range from mild symptoms such as fatigue, headache, shortness of breath to serious, life threatening conditions like opportunistic infections, deep venous thrombosis, pulmonary embolism, pneumothorax and lung fibrosis. A single center, prospective, observational study was carried out in a tertiary respiratory care institute in North India from June 2021 to August 2021 where 224 cases of previously treated COVID-19/ongoing symptomatic COVID-19 (those patients who were manifesting symptoms beyond 4 weeks), were enrolled and followed up for a period of 3 months to estimate the prevalence of persistent symptoms, complications and any risk factors associated with it. Data analysis was done using SPSS software version 21. Univariate and multivariate analysis done among risk factors and outcome variables. ROC was done on predictor variables and area under curve (AUC) calculated. p value less than 0.05 was considered significant. Among the 24.6% symptomatic patients at follow up, the most common symptom was fatigue (51.8%) followed by dyspnea (43.8%) and anxiety (43.3%). Among the complications of COVID-19, the most common according to our study was fibrosis (15.2%), followed by pulmonary thromboembolism (PTE) (12.1%), echocardiographic abnormalities (11.2%) and pulmonary mucormycosis (5.4%). Female gender, presence of comorbidities, requirement of non-invasive or invasive ventilation during hospital stay emerged as independent risk factors for complications following COVID-19. This study brings forth the huge morbidity burden that COVID-19 brought upon seemingly cured individuals and lists the risk factors associated with persistence of symptoms and complications. This would help to better streamline health resources and standardize follow up guidance of COVID-19 patients.

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Introduction

COVID-19 first appeared in Wuhan, China on December 31, 2019 and has affected ~469 million people worldwide and resulted in ~6 million deaths as of March 21, 2022 [1]. On January 30, 2020 India reported its 1st case of COVID-19 in Kerala [2], and has since reported ~43 million cases till March 21, 2022 [3]. While the world was still busy battling active infections, a plethora of patients started showing prolongation of symptoms or developing complications following an initial recovery. The NICE guideline classifies long Covid as: Acute COVID where a patient manifests symptoms up to 4 weeks; Ongoing symptomatic COVID where a patient manifests symptoms beyond 4 weeks and up to 12 weeks; and post-COVID

where a patient manifests symptoms for more than 12 weeks [4]. In these guidelines, the term "long COVID" comprises both subgroups, i.e., ongoing symptomatic COVID and post-COVID syndrome [4]. Post-COVID complications range from mild symptoms such as fatigue, headache, shortness of breath to serious, life threatening conditions like opportunistic infections, deep venous thrombosis, pulmonary embolism, pneumothorax and lung fibrosis [5]. The pathophysiology of long covid is both complex and poorly understood. It is postulated that an increase in the number of ACE-2 receptors is responsible for the spread of the virus throughout the body, wherein it produces proinflammatory and profibrotic responses, thus leading to the various complications [6]. Steroid therapy given for the treatment of COVID-19 has its own pros and cons. Corticosteroids have significant anti-inflammatory and anti-fibrotic effects, which may play a role in reducing pulmonary inflammation, especially in severe pneumonia and in advanced stages of COVID-19 disease [7]. It can also precipitate a lot of side effects including fatigue, myopathy, fluid retention, hyperglycemia, hypertension, psychological effects, weight gain, increased risk of infections, osteoporosis, *etc*. [8]. The British Thoracic Society guidelines recommend all patients hospitalized for COVID-19 get a chest roentgenogram done three months after discharge. Thorough clinical review and investigations are required for those with moderate or severe disease, persisting symptoms or with radiological abnormalities [9]. Chest radiography can be helpful in referring patients to respiratory clinics for investigations of persisting lung abnormalities and thromboembolic disease [10]. There is a lacuna in literature of studies looking at prevalence of morbidity following COVID-19, especially in the Indian subcontinent. Keeping in mind the myriad complications following COVID-19 and involvement of almost every organ system , this study was conducted to study the symptomology of patients following COVID-19 and its complications and any risk factors associated with it.

Materials and Methods

A single center, prospective, observational time bound study was carried out from June 2021 to August 2021 in the Department of Respiratory Medicine, at Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, India. Two hundred and twenty-four (224) consecutive cases of previously treated COVID-19/ongoing symptomatic COVID-19 (those patients who were manifesting symptoms beyond 4 weeks), above 18 years of age, belonging to both sexes were included in the study. Detailed history regarding current symptoms, previous symptoms, previous treatment, risk factors and comorbidities was taken. All necessary investigations were carried out which included hematological and radiological workup of the patient. The patients were then followed up monthly, up to3 months. Patient reported outcomes like tiredness, fatigue, pain, anxiety and depression were collected using the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue scale [11]. For shortness of breath, the Modified Medical Research Council (MMRC) scale was used [12]. Hematological investigations included blood investigations like Complete haemogram, kidney function test, liver function test, serum electrolytes, D-dimer, procalcitonin, ferritin and IL-6. The patients underwent cardiological examination followed by ECG and echocardiography. All patients routinely underwent HRCT Thorax both at the time of enrolment and at the end of the study to quantify presence or absence of fibrosis. Other specialized investigations like fiberoptic bronchoscopy guided biopsy or endoscopic biopsy by otorhinolaryngologists for suspected pulmonary or rhinocerebral mucormycosis were carried out as per requirement. In diagnosed cases of mucormycosis, brain MRI was also done to rule out cerebral mucor. For suspected cases of pulmonary embolism, CT pulmonary angiography was also done and in some suspected cases of myocarditis, cardiac MRI was done.

Statistical analysis

Statistical analyses were done with the help of SPSS version 21 and qualitative and quantitative analysis done. Univariate and multivariate analyses were done between certain pre-determined risk factors like age, female gender, number of comorbidities, etc. and persistence of the number of symptoms. Similar analyses also done between those risk factors and clinical signs of morbidity like persistence of fibrosis on CT scan, echocardiographic abnormalities, mucormycosis and pulmonary thromboembolism. Since cognitive dysfunctions and psychiatric abnormalities were common in post covid patients, ROC curve analysis was done to see the predictive power of our model with respect to anxiety and fatigue.

Results

The mean age of the study population was 46.8±13.14 years. When the gender distribution was examined, it was discovered that 63.3% of males were affected by COVID-19 complications. The majority of patients who developed complications had no prior comorbidity (64.3). Diabetes mellitus (DM) was the most common named comorbidity (14.3%), followed by chronic obstructive pulmonary disease (COPD) (11.2%), hypertension (9.8%), ischemic heart disease (IHD) (6.7%), and chronic kidney disease (CKD) (4.9%). Smoking and alcoholism were found in 41.9% and 44.2% of the patients respectively. The protective role of vaccination was established by the fact that among the ones who had received at least one dose of vaccine, only 11.2% developed complications. The mean duration of hospitalization for the patients was 32.9±15.8 days. Among the hospitalized patients, 42.2% had history of admission in the Intensive Care Unit (ICU). Most of the patients requiring oxygen were put on face mask (57.6%), followed by invasive mechanical ventilation (17.4%), high flow nasal oxygen (13.8%), and non-invasive ventilation (11.2%). It was observed that after getting discharged from the hospital, 75.4% of the patients remained asymptomatic on follow up visits until 3 months, while 24.6% of the patients were either symptomatic/developed complications on the first follow up visit or eventually turned symptomatic/developed complications on the subsequent visits. The patients presented with an array of symptoms/complications, the most common of which was fatigue (51.8%). Figures 1 and 2 depict the various symptoms/complications the patients presented with during the 3 month follow up period. Univariate and multivariate analysis was done to look for an association between the risk factors and the symptomatology at presentation which revealed age (p£0.003), female gender (p£0.002), number of co-morbidities (p£0.001), history of ICU admission (p£0.009), length of hospitalization (p£0.001), requirement of non-invasive ventilation (p£0.001), requirement of invasive mechanical ventilation (p£0.002) and vaccination status (p£0.003) to be independent risk factors. While BMI (p£0.4) and requirement of high flow nasal cannulation (p£0.06) failed to show

a statistically significant association (Table 1). Since cognitive dysfunctions and psychiatric abnormalities were common in post covid patients, ROC curve analysis was done to see the predictive power of our model with respect to anxiety and fatigue and it revealed an area under the curve of 0.9 and 0.97, respectively (Figures 3 and 4). A multiple logistic regression between risk factors and clinical complications revealed female gender, number of co-morbidities, history of ICU admission, length of hospitalization, requirement of non-invasive ventilation and requirement of invasive mechanical ventilation to be independent risk factors for the development of pulmonary thrombo-embolism. Age, number of co-morbidities and requirement of invasive mechanical ventilation to be independent risk factors for the echocardiographic abnormalities. Age, number of co-morbidities, requirement of invasive mechanical ventilation and vaccination status to be independent risk factors for the persistence of fibrosis at follow up scans while female gender, number of co-morbidities, history of ICU admission, length of hospitalization, requirement of non-invasive ventilation, requirement of invasive mechanical ventilation and vaccination status were independent risk factors for the development of mucormycosis (Table 2).

Discussion

A study conducted by Murhekar *et al.* [13] demonstrated that seroprevalence of COVID-19 ranged between 0.62-1.03% in India. The COVID-19 pandemic has affected millions of people worldwide leaving a huge burden of long-term care in the survivors of this fatal disease. Post-COVID syndrome is a multisystem disease occurring after the acute illness of COVID-19 [14], occurring 4 weeks after the diagnosis of COVID-19 [15].

COVID-19 is associated with the release of pro-inflammatory cytokines like IL-6, IL-1 and TNF-α. These cytokines are responsible for an increase in the levels of tissue factor that has procoagulant

Table 1. Univariate and multivariate analysis between risk factors and total number of symptoms at follow up.

Risk factors	Univariate analysis (test used)	p-value	Multivariate analysis	
			p-value	Estimates
Age	Pearson's correlation	0.003	0.005	0.09
Female gender	Student's *t*-test	0.002	0.0016	0.97
BMI	Pearson's correlation	0.04	0.63	0.62
No of comorbidities (one)	Student's *t*-test	0.001	0.01	1.43
No of comorbidities (two)	Student's *t*-test	0.003	0.004	2.20
ICU admission	Student's *t*-test	0.009	0.04	0.48
Length of hospitalization	Pearson's correlation	0.001	0.02	0.016
Requirement of HFNO	Student's *t*-test	0.03	0.81	0.06
Requirement of NIV	Student's *t*-test	0.001	<0.0001	2.63
Requirement of IMV	Student's *t*-test	0.002	<0.0001	2.99
Not COVID vaccinated	Student's *t*-test	0.003	0.02	0.79

BMI, body mass index; ICU, intensive care unit; HFNO, high flow nasal oxygen; NIV, non-invasive ventilation; IMV, intermittent mandatory ventilation.

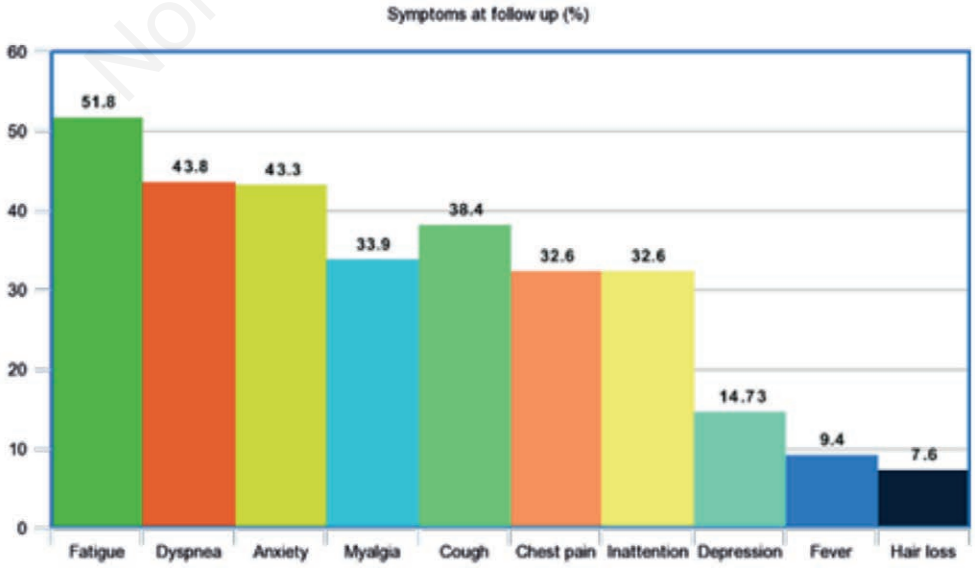

Figure 1. Histogram representing symptoms at follow up in patients recovered from COVID-19.

affect, thus increasing risk of thromboembolism. They are also responsible for causing inflammation that leads to pulmonary fibrosis and lung damage resulting in fatal outcomes [6,16]. The main aspect of the pathophysiology of COVID-19 is ACE-2 receptors. They are increased in number in the various tissues and allows the spread of virus throughout the body. As SARS-CoV-2 virus enters the various organs, there is internalization of ACE-2 receptors, hence an increase in free circulating angiotensin-2, that results in vasoconstriction, proinflammatory, profibrotic response, *etc*. [17].

In our study the mean age of the study population was 46.8±13.14 years, which shows a relatively younger population when compared to the studies [18,19] conducted in the west where the mean age of the study population was 59.6±14.0. This younger predisposition in our study could be attributed to the fact that in India the vaccines to the younger population were made available later in the course of the pandemic accounting for a large number of seronegative individuals in this age group. On analysing the gender distribution, it was observed that 63.3% males were affected with complications of COVID-19 which was similar to the studies conducted by Sykes [18] and Aul [19] where 65.7% and 56.6% of the subjects respectively were males.

Most patients in our study who developed post-COVID symptoms did not have any pre-existing comorbidities (64.3%), which was similar to a study done by Kamal *et al*. [20] which also showed that COVID-19 was an independent risk factor for most of the complications as 70.7% did not have any pre-existing comorbidities. Among the named complications the most common was DM followed by hypertension and COPD, two other studies conducted by Sykes [18] and Kamal [20] showed that the most common comorbidity was hypertension followed by DM. In our study 42.2% had history of ICU admission. Sykes [18] and Van Aerde [21] in their studies showed that around 20% of the patients with COVID-19 who had developed complications had been admitted to the ICU. A study conducted by Taboada [22] hypothesized that

Table 2. Multiple logistic regression between risk factors and clinical complications.

Risk factors	Pulmonary thromboembolism		Echocardiographic abnormalities		Persistence of fibrosis at follow up	Mucormycosis		
	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)
Age	0.3	-	0.003	12.1 (16.1-8.1)	0.01	6.2 (7.2-5.2)	0.8	-
Female gender	0.02	2.3 (3.2-1.4)	0.08	-	0.7	-	0.01	6.2 (7.2-5.2)
BMI	0.6	-	0.35	-	0.6	-	0.6	-
No of comorbidities (one)	0.2	-	0.12	-	0.02	4.8 (5.4-4.2)	0.03	4.3 (5.2-3.4)
No. of comorbidities (two)	0.04	2.2 (3.1-1.3)	0.02	4.3 (6.2-2.4)	0.008	12.3 (16.6-8)	0.001	9.2 (12.2-6.2)
ICU admission	0.02	2.6 (3.6-1.6)	0.06	-	0.63	-	0.01	5.4 (6.2-4.6)
Length of hospitalization	0.03	2.4 (4.2-0.6)	0.36	-	0.53	-	0.001	11.3 (14.3-8.3)
Requirement of HFNO	0.8	-	0.73	-	0.8	-	0.2	-
Requirement of NIV	0.04	2.1 (3.6-0.6)	0.24	-	0.62	-	0.02	3.9 (5.2-3.6)
Requirement of IMV	0.01	4.1 (5.2-3)	0.01	7.6 (9.6-5.6)	0.02	4.5 (7.2-1.8)	0.01	4.3 (6.2-2.4)
Not COVID vaccinated	0.2	-	0.29	-	0.04	2.1 (3.1-1.1)	0.01	4 (5.2-2.8)

BMI, body mass index; ICU, intensive care unit; HFNO, high flow nasal oxygen; NIV, non-invasive ventilation; IMV, intermittent mandatory ventilation.

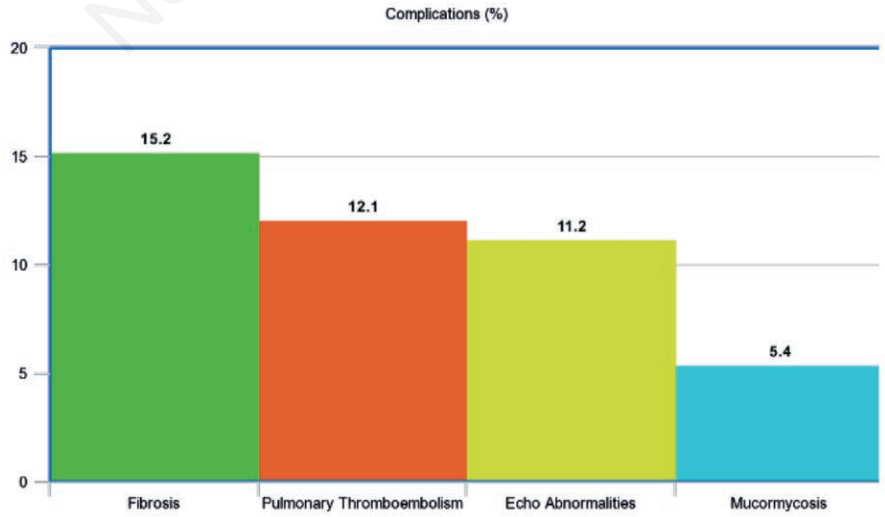

Figure 2. Histogram representing complications in patients recovered from COVID-19.

patients with prolonged duration of hospitalization, history of ICU admission and invasive mechanical ventilation were more likely to suffer from long term tissue damage and persistent symptoms. In our study most patients required oxygen therapy in the form of facemask (57.6%), followed by invasive mechanical ventilation (17.4%), high flow nasal oxygen (HFNO) (13.8%) and non-invasive mechanical ventilation (11.2%) which was consistent with the findings of the study by Sykes [18] that showed the requirement of facemask to be 59.4% followed by room air and HFNO, at 13.4% each, invasive mechanic ventilation (6.7%) and NIV (5.9%).

The most common symptom at follows up in our study was fatigue followed by dyspnoea. A post-acute COVID-19 outpatient service established in Italy [22] reported fatigue (53.1%), dyspnoea (43.4%), joint pain (27.3%) and chest pain (21.7%) as the most reported symptoms at 60-day follow up which was consistent with our study. In a prospective cohort study from Wuhan, China,[24] long-term consequences of acute COVID-19 were evaluated by comprehensive in-person evaluation of 1,733 patients at 6 months from symptom onset. The majority of the patients (76%) reported at least one symptom, fatigue being the most common (63%), followed by sleep difficulties (26%) and anxiety/depression (23%).

Among the complications of COVID-19, the most common according to our study was fibrosis, followed by pulmonary thromboembolism (PTE), echocardiographic abnormalities and pulmonary mucormycosis which was consistent with another study conducted by Aul [19] according to which post covid fibrosis was seen in 9.3% of the patients, followed by PTE (1.6%), echo abnormalities i.e., left ventricular dysfunction (1.3%) and pulmonary artery hypertension (2.3%).

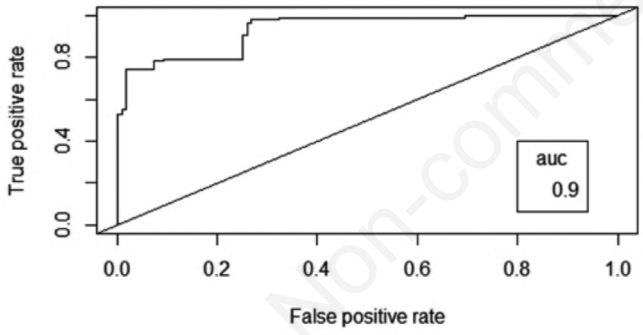

Figure 3. ROC curve of risk factors to predict presence of fatigue.

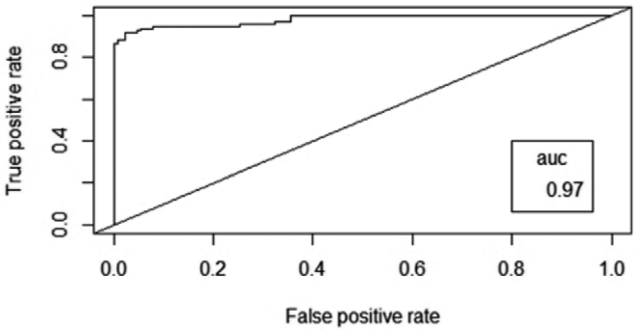

Figure 4. ROC curve of risk factors to predict presence of anxiety.

Conclusion

There are numerous complications that occur in patients recovered from previously treated COVID-19 disease. This study enumerates many of the symptoms and complications that follow the infection and the factors associated with the disease. The protective role of vaccination was also established in this study. This study is one of the few studies that establish the various predictors of post COVID complications in patients admitted with moderate to severe COVID symptoms. We believe that larger studies would help us better understand the pathophysiology of post COVID-19 symptoms and complications, its morbidity burden and risk factors associated with it. This would lead to better management of complications and streamline health care resources.

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