



## One Year Follow Up Study Of Covid - 19 Patients Admitted To Tertiary Care Hospital - A Prospective Observational Cohort Study

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### ABSTRACT

**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is responsible for the current coronavirus disease 2019 (COVID-19) pandemic that has affected more than 170 million people worldwide. The etiology and pathophysiology of long COVID still needs to be clearly defined. Patients with long COVID present with prolonged multisystem involvement and significant disability. To understand better the long-term course and etiology of symptoms, we analyzed a cohort of patients with COVID-19 prospectively. The subjects were followed up at 3, 6 and 12 months after discharge from the hospital.

**Objectives:** (i) To study the symptoms and co-morbidities in patients with COVID 19, after discharge from hospital at 3rd, 6th and 12<sup>th</sup> month.

(ii) To study the pulmonary complications in patients with COVID-19 after discharge from hospital at 3rd, 6th and 12<sup>th</sup> month.

(iii) To study the lung function (FEV1, FVC, PEFr) in patients with COVID-19 after discharge from hospital at 3rd, 6th and 12<sup>th</sup> month

**Methods:** About 90 COVID -19 patients who were admitted during March 2021 to June 2021 were prospectively followed up at 3,6 and 12 months after discharge to find the persistence of symptoms and status of comorbidities. They were also examined for the development of any pulmonary complications and their pulmonary function tests were done at 3, 6 and 12 months of follow up.

**Results:** Our study shows a significant increase in the comorbidities like diabetes mellitus and COPD from the time of admission till the time of follow up at one year. It was seen that at the time of admission about 34% of patients had diabetes mellitus, which further increased to 55.2%, 66.7% and 70.1% respectively at three months, six months and one year of follow up. Also, there was persistence of symptoms like cough, shortness of breath, headache and fatigue on follow up at 3,6 and 12 months. As far as pulmonary complications are concerned it is seen that 40.2%, 35.9%, 37.7% of the subjects developed viral infections at 3 months, 6months and 1 year respectively.

**Conclusion:** Our study found a significant increase in comorbidities like type 2 diabetes mellitus, increase in respiratory complications and persistence of symptoms like fatigue in patients who suffered from COVID-19 infection on follow up.

**Key words:** COVID-19, symptoms, comorbidities, fatigue, pulmonary, complications

### **Introduction:**

In December 2019, a new virus was found to be causing severe respiratory illness that is COVID 19 infection, initially seen in China which later spread globally to cause COVID-19 pandemic. WHO declared COVID-19 as global pandemic on 11th March 2020.<sup>1</sup> Most of the patients were asymptomatic or mildly symptomatic causing upper respiratory tract infection. Majority of the patient also had moderate, severe and very severe pneumonia,<sup>2</sup> requiring hospital admission and prolonged hospital stay. COVID-19 pandemic has put lot of impact in terms of financial, physical, emotional, health infrastructure and way of living. Millions of people in the world were confirmed with COVID -19 infection, many of them stayed in hospital for longer duration for treatment and isolation and to prevent further spread of disease. Many patients died due to severe infection and the complications associated with the

disease. Studying the long-term outcome of COVID-19 disease, it is very difficult to understand the natural history of disease, requiring regular follow up of patients.<sup>3</sup>

Many of patients who were infected, recovered from their presenting symptoms with the available treatment and a few more developed new symptoms during hospital stay and after discharge. On regular follow up, it was noted that some patients had developed relapsing post COVID -19 symptoms like extreme fatigability.<sup>4</sup> Patients with COVID-19 are more likely to demonstrate multiple organ effects, leading to multiple pulmonary and extrapulmonary manifestations<sup>5</sup> including thrombotic complications<sup>6</sup>, endocrine, neural (psychological), and cardiovascular systems.<sup>7-11</sup> However, long-term follow-up studies investigating multiple organ function in recovered patients are lacking in Indian population. Hence this study was taken up to follow up the COVID-19 patients at 3,6 and 12 months for the development of comorbidities, persistence of symptoms, development of pulmonary complications and testing the pulmonary functions using FEV1, FVC and PEFr.

### **Materials and Methods:**

This is a prospective observational study conducted in tertiary care hospital in Bangalore, from March 2021 to June 2021. All patients above 18 years of age who were diagnosed with COVID- 19 infection and confirmed for COVID-19 on RT-PCR (Reverse transcriptase-polymerase chain reaction), admitted to our tertiary care hospital and gave informed consent were included for the study. Those below 18 years, not willing to participate in the study, patients transferred to another healthcare facility, patients who did not attend a single follow up were excluded from the study.

A total of 90 subjects were included in the study at the time of admission of which 3 patients were lost to follow up at 3 months, 12 patients at 6 months and 1 year and one patient died. Hence 87, 78 and 77 subjects were available for follow up at 3,6 and 12 months respectively. At admission, details like demographic characteristics, presence of co-morbidities, laboratory data, and medical details were collected by taking history and the patient's previous hospital records. Disease severity was classified into the four severity grades from the clinical guidance for COVID-19 pneumonia diagnosis and treatment, issued by WHO.<sup>12</sup> All discharged patients met uniform discharge standards: no fever for three consecutive days, improved respiratory symptoms, obvious recovery of acute lung lesions, and two negative SARS-CoV-2 test results, 24 hours apart. The patients were contacted by a research assistant

in the order of their recorded discharge date. History, respiratory and other symptoms evaluation, respiratory function testing (spirometry and PEFR), relevant blood investigations were evaluated in the outpatient clinic at 3rd, 6th and 12th month after discharge between July 2021 to June 2022.

At admission, patient demographic data, height weight, co morbidity, disease clinical severity based on WHO guidelines<sup>12</sup> length of hospital stay were noted.

At the third month, sixth month and 12month, patients were contacted telephonically and advised for outpatient follow up. At each visit, all patients BMI was noted, symptoms were assessed, co-morbidities were noted and based on symptoms patients were subjected to relevant blood investigation (complete blood count, HbA1C thyroid function test etc), HRCT thorax, sputum culture sensitivity, sputum for AFB staining, 2D echo, ECG were done. Pulmonary hypertension was diagnosed based on 2D Echo. All patients were subjected to spirometry test -FEV1 and FVC and PEFR measurement as per ATS/ERS guidelines<sup>13</sup> at each follow up.

Respiratory system assessment was done on each follow up visit based on history, symptoms, clinical examination, HRCT thorax in selected patients, ECG and 2-dimension Echocardiography in selected patients was done by trained cardiologist. Respiratory infection was diagnosed based on clinical history, Complete blood count, sputum culture and sensitivity, AFB staining and Gene X pert MTB as per NTEP guidelines

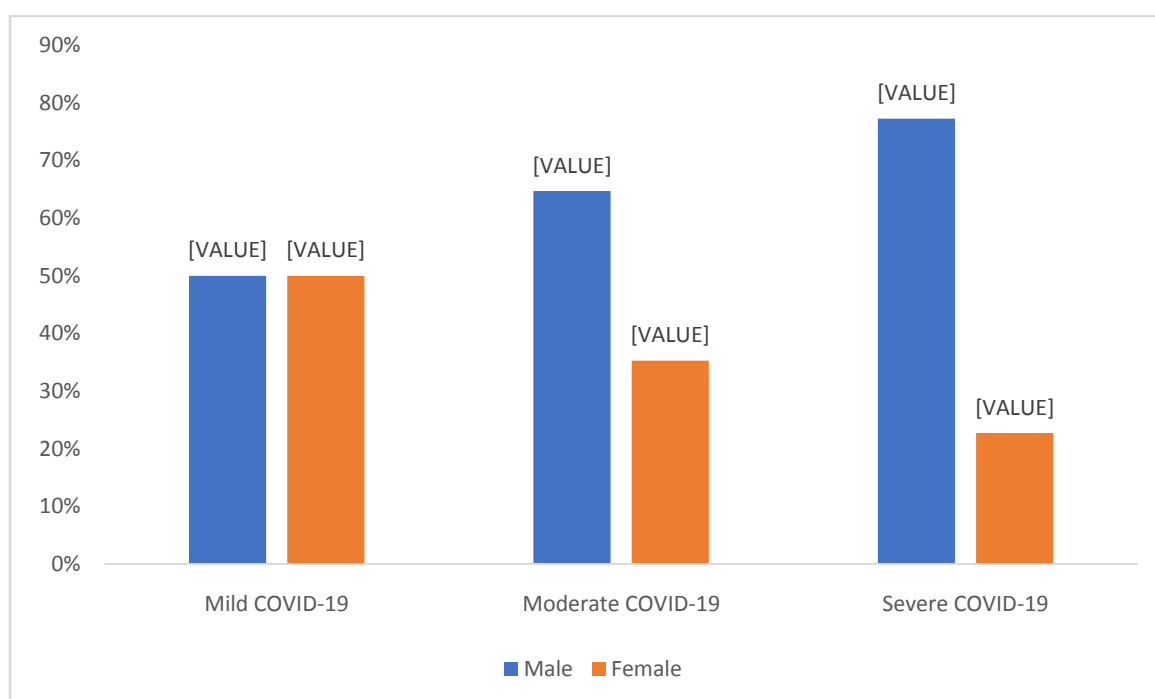
Respiratory function assessment was done using Helios spirometer as per ATS/ERS guidelines (3) at 3rd,6th and 12<sup>th</sup> month follow up with all safety and infection prevention protocol, FEV1(Forced expiratory Volume in 1second) and FVC (Forced vital capacity) were noted and was graded into Normal (>80%), Impaired / reduced (<80%). PEFR (Peak Expiratory Flow Rate) was measured using Pulmopeak peak flow meter(L/min) was arbitrarily classified as Normal(>350L/min) and Impaired (<350L/min).

## Statistical Analysis:

The collected data was tabulated in Microsoft excel and statistical analysis was done using software SPSS 22. Descriptive statistics was calculated and chi-square test was used to find the association between two variables.  $P < 0.05$  was considered statistically significant.

## Results

In our study, 90 patients were included of average age of 47.74 years (Range 18-88years) of which 62 patients were male and 28 patients were female.



**Figure1: COVID-19 patients according to gender and severity**

Figure 1 shows the gender wise distribution of COVID-19 patients at admission. It was seen that the gender wise distribution was equal in mild COVID, whereas for moderate and severe COVID a greater number of males (64.7% moderate, 77.3% severe) were affected compared to female.

**Table 1: Follow up of COVID-19 patients for comorbidities at three months, six months and 1 year**

Comorbidity	At admission (n=90)	Three months (n= 87)	Six months (n= 78)	One Year (n=77)	p value
<b>Diabetes mellitus</b>	31 (34.4%)	48 (55.2%)	52 (66.7%)	54 (70.1%)	<b>p &lt; 0.00001</b>
<b>Hypertension</b>	24 (26.7%)	32 (36.8%)	35 (44.9%)	35 (45.4%)	p = 0.932
<b>IHD</b>	7 (7.8%)	9 (10.3%)	8 (10.2%)	10 (12.9%)	p = 0.746
<b>COPD</b>	4 (4.4%)	6 (6.9%)	18 (23.1%)	23 (29.9%)	<b>p &lt; 0.00001</b>
<b>Bronchial Asthma</b>	6 (6.7%)	7 (8%)	8 (10.2%)	10 (12.9%)	p = 0.528
<b>Epilepsy</b>	4 (4.4%)	4 (4.6%)	4 (5.1%)	4 (5.2%)	p = 0.994
<b>CVA</b>	5 (5.6%)	13 (14.9%)	11(14.1%)	12 (15.6%)	p = 0.148
<b>Hypothyroidism</b>	17 (18.9%)	18 (20.7%)	18 (23.1%)	19 (24.7%)	p = 0.811
<b>Chronic Kidney disease</b>	2 (2.2%)	4 (4.6%)	7 (8.9%)	7 (9.1%)	p = 0.165
<b>Obesity</b>	34 (37.8%)	33 (37.9%)	32(41%)	32(41.5%)	p = 0.993
<b>Hypercholesterolemia</b>	0	0	4(5.1%)	9 (11.7%)	p = 0.140

Note: Total number could not be given as many subjects had multiple comorbidities

Table 1 shows that there was a significant increase in the comorbidities like diabetes mellitus and COPD from the time of admission till the time of follow up at one year. It was seen that at the time of admission about 34% of patients had diabetes mellitus, which further increased to 55.2%, 66.7% and 70.1% respectively at three months, six months and one year of follow up. Similarly, history of COPD was present in 4.4% of patients at admission which further increased to 6.9%, 23.1% and 29.9% at 3 months, 6 months and one year of age. There was no significant increase in other comorbidities like IHD, bronchial asthma, epilepsy, CVA, hypothyroidism, chronic kidney disease, obesity and hypercholesterolemia was no significant increase in other comorbidities like IHD, bronchial asthma, epilepsy, CVA, hypothyroidism, chronic kidney disease, obesity and hypercholesterolemia.

**Table 2: Symptoms in COVID-19 patients at three months, six months and 1 year**

Symptoms	At admission (n=90)	Three months (n= 87)	Six months (n= 78)	One Year (n=77)
<b>Cough</b>	88 (97.8%)	22 (25.3%)	19 (24.3%)	14 (18.2%)
<b>Shortness of breath</b>	87 (96.7%)	27 (31%)	27 (34.6%)	20 (25.9%)
<b>Fever</b>	85 (94.4%)	0 (0%)	0 (0%)	2 (2.6%)
<b>Chest pain</b>	35 (38.9%)	3 (3.4%)	1(1.3%)	0
<b>Palpitations</b>	27 (30%)	2 (2.3%)	3 (3.8%)	2(2.6%)
<b>Sore throat</b>	20 (22.2%)	1 (1.1%)	1 (1.3%)	1(1.3%)
<b>Headache</b>	15 (16.7%)	2 (2.3%)	3 (3.8%)	1(1.3%)
<b>Fatigue</b>	70 (77.8%)	40 (45.9%)	30 (38%)	29 (37.7%)
<b>Loss of taste</b>	13 (14.4%)	0	0	0
<b>Loss of smell</b>	11 (12.2%)	0	0	0
<b>Diarrhoea</b>	21 (23.3%)	0	0	0

**Note: Total number could not be given as many subjects had multiple symptoms**

Table 2 shows that there was persistence of symptoms like cough, shortness of breath, headache and fatigue on follow up at 3,6 and 12 months whereas loss of taste (14.4%), loss of smell (12.2%) and diarrhoea (23.3%) were present only at the time of admission. The most common persistent symptom was fatigue which was seen in 45% of the subjects at 6 months and 37% subjects at 1 year of follow up, this was followed by shortness of breath which was persistent in 31%, 34.6% and 25.9% of subjects at 3,6 and 12 months of follow up.

**Table 3: Pulmonary complications in COVID -19 patients at 3, 6 and 12 months of follow up**

Pulmonary complications		Three months (n= 87)	Six months (n= 78)	One Year (n=77)
Fibrosis		6 (6.9%)	9 (11.5%)	5 (6.5%)
Pulmonary arterial hypertension (PAH)		3(3.4%)	5 ((6.4%)	6(7.8%)
Congestive cardiac failure (CCF)		3 (3.4%)	5 (6.4%)	7 (9.1%)
Respiratory infections	Bacterial	24 (27.6%)	26 (33.3%)	18 ((23.4%)
	Viral	35 (40.2%)	28 (35.9%)	29 (37.7%)
	Fungal	1(1.1%)	0	0
	TB	0	1 (1.3%)	5 (6.5%)

**Note: Total number could not be given as many subjects had multiple complication**

Table 3 shows the development of pulmonary complications in COVID patients on follow up at 3,6 and 12 months. The most common complication is development of viral infections followed by bacterial infections. It is seen that 40.2%, 35.9%, 37.7% of the subjects developed viral infections at 3 months, 6months and 1 year respectively. Other complications like fibrosis, pulmonary arterial hypertension and CCF were also seen to occur. 11.5% of the subjects developed fibrosis at 6 months of follow up, 7.8% were seen to develop PAH at one year and 9.1% developed CCF at 1 year of follow up. It was also seen that about 6.5% of the subjects were found to be positive for pulmonary TB at 1 year of follow up.



**Table 4: Pulmonary function test in COVID-19 patients at three months, six months and 1 year**

Pulmonary Function Test		3 months (n= 87)	6 months (n=78)	1 Year (n = 77)
FEV <sub>1</sub>	> 80%	29 (33.3%)	29 (37.2%)	28 (36.4%)
	< 80%	58 (66.7%)	49 (62.8%)	49 (63.6%)
FVC	>80%	33 (37.9%)	30 (38.5%)	30(39%)
	< 80%	54 (62.1%)	48 (61.5%)	47 (61%)
PEFR	<350	70 (80.5%)	56 (71.8%)	54 (70.1%)
	> 350	17 (19.5%)	22 (28.2%)	23 (29.9%)

Table 4 shows the results of the pulmonary function test done at 3, 6 and 12 months of follow up. It is seen that the FEV<sub>1</sub> is < 80% in 66.7% of the subjects at 3 months, 62.8% at 6 months and 63.6% at 1 year. The FVC values are < 80% in 62% of the subjects at 3 months. The PEFR is 350 in < 80.5% of the subjects at 3 months and 70.1% of the subjects at 1 year of follow up.

## Discussion

In our study it was seen that the gender wise distribution was equal in mild COVID, whereas 64.7% males and 35.3% females suffered from moderate COVID-19 infection. These findings were similar to the findings of a study done by S Kushwaha et al<sup>14</sup> in which 65.39% males and 34.61% females had COVID-19 infection.

The possible reason for more males being affected compared to females could be women's lower access to healthcare due to social norms, financial and non-financial barriers which may affect women's testing for COVID-19 and access to adequate care, and result in underreported female cases a from COVID-19.

Our study shows that 97.8% of the subjects had cough at admission on following up at 3 months about 25.3% of the subjects had cough. 94.4% of the subjects had fever and 77.8% had fatigue. Whereas only 14.4% and 12.2% presented with loss of taste and smell respectively. At follow up on 3, 6 and 12 months it was found that the most common

persistent symptom was fatigue which was present in 45.9% of the subjects on follow up at 3 months and 37.7% at end of 1year.

Similar findings were found in a study done by A Daher et al <sup>15</sup> where the most common symptoms on admission were cough and fever seen in 70% and 60% of the subjects. 64% of the subjects presented with fatigue on admission which was the most persistent symptom found in 45% of the subjects on follow up at 33 days.

In our study, Diabetes mellitus was recorded in 34.4% patient at admission and 70.1% at the end of the one-year period, which was significant, probably may be due to use of steroids for treatment of COVID patients.<sup>16</sup> similar significant results were obtained in a study by Daniel Ayoubkhani et al. <sup>7</sup>

Our study showed COPD in 4.4% cases at admission and 29.9% patients at the end of one year follow up, ( $p < 0.00001$ ) which was significant, may be due to Viral infection is risk factor for precipitating underlying COPD <sup>17</sup>, similar findings was seen in study by Daniel Ayoubkhani et al. <sup>7</sup> were in increase rate of respiratory disease ( $p < 0.0001$ ).

Other finding in our study were increase in hypertension 35(45.4%) at the end of 1year compared to 24(26.7%) at admission, probably may be multifactorial, due to sedentary life style due to COVID imposed lock down and medication use. Obesity was seen in 32(41.5%) at end of 1year follow up, Cerebro vascular accidents in 12(12.9%) may be multifactorial and due to use of anticoagulants in COVID -19 treatment as COVID infection raised the incidence of thrombo embolic events.<sup>18</sup>

The monitoring of patients who recovered from COVID-19 pneumonia demonstrated association with lung fibrosis during follow up and associated with negative prognosis. our study showed lung fibrosis in 6.9%, 11.5% and 6.5% of patients with moderate to severe disease at 3rd, 6th 12th month respectively, which is very less probably because we screened only symptomatic patients with CT. A study by Fu Z., et al <sup>19</sup> showed lung fibrosis in 56% of patients with moderate disease. According to Vasarmidi et al <sup>20</sup> and Rai et al <sup>21</sup> rate of COVID fibrosis may exceed 30%. In four patients we noticed that there was regression in pulmonary fibrosis at the end of 1 year, hence its will be interesting to know any antifibrotic drug might help in treating lung fibrosis which needs further research.

Pulmonary hypertension was seen in 3.4% at 3<sup>rd</sup> month and 7.8% at the end of one-year. Congestive cardiac failure was seen in 3.4% at 3<sup>rd</sup> month and 9.1% at the end of one year.

The probable reason for this may be due to repeated lung infection causing decline in lung function and associated lung fibrosis in patient with covid 19 Pneumonia.

One year follow up of post COVID-19 pneumonia patients showed increased risk of viral infections (40.2%) Versus Bacterial infection (27.6%) at 3rd month follow up, similar results were obtained at 1 year follow up viral infection seen in 37.7% Versus Bacterial infection seen in 23.4% patients. Five Patients (6.5%) were diagnosed with tuberculosis at the end of one year follow up. Increased risk of respiratory infections was also noted in study conducted by Daniel Ayoubkhani et al.<sup>7</sup> and similar increased risk of repeated infection was also noted in past, after SARS and MERS infections in studies done by hui GS<sup>22</sup> and Darcis G et al.<sup>23</sup> Probable reason might be due to impaired local immunity after a moderate to severe Covid 19 infection and use of steroids during treatment.

Our study showed FEV1 is < 80% in 66.7% of the subjects at 3 months, 62.8% at 6 months and 63.6% at 1 year. The FVC values are < 80% in 62% of the subjects at 3 months. The PEFr is < 350 in 80.5% of the subjects at 3 months and 70.1% of the subjects at 1 year of follow up, Which in contrast to studies done by Darcis G et al<sup>23</sup> and Li Di et al<sup>24</sup> where only around 21.8% patients had FEV1 < 80% and 27.5% patients had FVC < 80%.

Our study showed persistence of symptoms after discharge following COVID-19 pneumonia, fatigue being most common. Increased prevalence of diabetes, COPD which might develop over period of time hence regular follow up of patients is required to detect and treat early. Persistent symptoms during follow up need evaluation to rule out lung fibrosis and other infection. After discharge patients develop pulmonary and extra pulmonary manifestations, hence multisystem approach is advised and needs the proper recommendation and further studies to approach patients of COVID-19 holistically.

Limitations of the study were that our study had patients enrolled at a single-center, some patients were lost to follow up and the baseline patient data, such as pulmonary function tests, were unavailable at admission as they were not performed in the COVID-19 patients due to the risk of cross infection.

In conclusion, long term manifestations of Covid 19 should not be neglected, which will help us to understand the natural history of Covid 19 pneumonia better, hence regular follow up of patients become mandatory to detect and treat complication early which will help us to reduce burden on health care system and to reduce long term effects on multi organ.

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