Original Article

A Study to Evaluate Post COVID-19 Manifestations - An Observational Study

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ABSTRACT

Introduction : The epidemiological, clinical characteristics, pathogenesis, and complications of patients with COVID-19 at acute phase have been explicitly described, but the long-term consequences of the illness remain largely unclear. The survivors of the pandemic suffer from myriad health problems ranging from depression to pulmonary fibrosis. Associated with the disease itself, as well as the collateral damage to the economy, these symptoms require periodic assessment and follow up. This study aims to investigate and characterize the manifestations which appear after eradication of the acute corona virus infection and its relation to the severity of the disease.

Methods : 200 patients discharged from COVID ICU in Tertiary Care Hospital in central India from July 1st 2020 to September 30 th 2020, were followed up for 3 months post discharge.

Results : High proportion of individuals reported fatigue (75.5%), dyspnea (70%), anosmia (55.5%) and myalgia (62%). The persistence of symptoms was significantly more in those with severe disease at onset.

Conclusion : At 3 months after acute infection, COVID-19 survivors were mainly troubled with fatigue and muscle weakness, altered taste and smell sensation. Patients who were more severely ill during their hospital stay had more severely impaired quality of life and are to be looked after for them to have an optimal long-term quality of life.

Introduction :

The total number of COVID-19 cases in India, (as of 10th January 2021) is 10.46 million, with 99% patients recovering from the acute infection. However, they are not completely asymptomatic, with new symptoms arising and persisting beyond the usual expected recovery time from this acute "flu - like illness". It is therefore necessary to perform comprehensive follow-up, to assess the health of these pandemic survivors at regular intervals and provide appropriate assistance to not only their physical health but also psychological condition. However, the information regarding the persistence of these symptoms in patients who were discharged from hospitals after recovery from COVID-19 is lacking.

Aim & Objectives :

1. To find out the persistent symptoms in patients after acute COVID-19.

2. To find out the occurrence of new symptoms in discharged patients after acute COVID-19.

3. To find out the long lasting effects of COVID-19 & its effect on patient's life.

Methods :

200 patients admitted to GMCH Nagpur during the period from July 1st 2020 to September 30th 2020, were followed up for 3 months post discharge.

Inclusion Criteria :

All patients who were RTPCR positive and admitted in Government Medical College & Hospital and were successfully discharged as per the World Health Organization criteria i.e.

- No fever for 3 consecutive days,

- Improvement in pre-admission symptoms,

- 2 Negative test results (RTPCR) for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] 24 hours apart).

Patients were offered a comprehensive medical assessment with detailed history and physical examination. Data on all clinical characteristics, including clinical and pharmacological history, lifestyle factors, and body measurements, were collected in a structured electronic data collection system.

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In particular, data on specific symptoms potentially correlated with COVID-19 were obtained using a standardized questionnaire administered at enrolment. Patients were asked to retrospectively recount the presence or absence of symptoms during the acute phase of COVID-19 and whether each symptom persisted at the time of the study. More than 1 symptom could be reported.

This study was approved by the Institutional Ethics Committee.

Written informed consent was obtained from all participants.

Results :

200 eligible patients were included in this study done during the period from July 1st 2020 to September 30th 2020.

The mean age of the patients was 33 years (range, 15-80 years), and 80 (40%) F and 120 (60%) M.

During hospitalization, 62.3% of participants had evidence of interstitial pneumonia. The mean length of hospital stay was 7 (2-24 days) days; 61 (30.5%) patients received 5-15L/min oxygen therapy, 18 patients (9%) received non-invasive ventilation (NIV) and 1 patient received HFNO. No patient received invasive ventilation. The characteristics of the study population are summarized in the *Table 1.* Diabetes and hypertension were the most common co-morbidities.

Patients were assessed at a mean of $60.3 + 13.6$ days after onset of the first COVID-19 symptom; at the time of the evaluation, only 2.5% were completely free of any COVID-19 related symptom, while 32.5% had 1 or 2 symptoms and 55% had 3 to 6 symptoms and 10% had 7 or more. The *Figure 2.* shows that a high proportion of individuals still reported fatigue (75.5%), dyspnea (70%), anosmia (55.5%) and myalgia (62%).

Table 1 : Clinical profile of COVID-19 patients included in study (N = 200)

Characteristics	Mean ± SD (Range) / Frequency (%)
Age in years	33 ± 16.08 (15 - 80)
Sex (M/F)	120/80 (1 : 0.67)
BMI (Mean ± SD) BMI>25	24.24 ± 2.40 (18-32) 53 (26.5)
Co-morbidities (Patients had multiple co-morbidities) Hypertension Diabetes BA IHD CVE Hypothyroidism PTB Psychiatric (SDH) RTA	19 (9.5%) 12 (6%) 7 (3.5%) 5 (2.5%) 2 (1%) 5 (2.5%) 2 (1%) 2 (1%) 4 (2%)
Smoking	47 (23.5%)
No comorbidites	128 (64%)
Median hospital stay (in days)	7 (2 - 24)

Fig. 1 : Co-morbidities of patients in the study
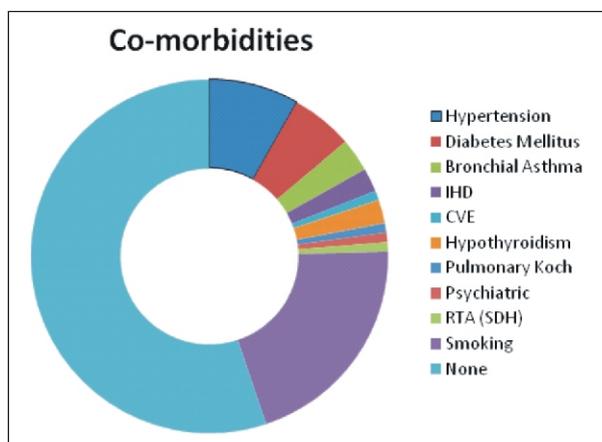

Table 2 : Oxygen requirement of patients during Acute COVID 19 infection.

Oxygen requirement (N=61)	61(30.5)
Median (IQR) in litre	8 (6 - 15)
Median (IQR) in days	10 (5 - 15)
NIV	18 (9.0)
HFNO	1 (0.5)
INTUBATED	NIL

(NO PATIENT HAD OXYGEN REQUIREMENT ON DISCHARGE)

Table 3 : **CT severity score of patients in study on admission and discharge**

Chest CT severity score (N=200)	At admission	At discharge
0 - 5 (137)	137 (68.5 %)	150 (75%)
6 - 10 (31)	31 (15.5 %)	35 (17.5%)
11 - 15 (23)	23 (11.5%)	10 (5.5%)
16 - 25 (9)	9 (4.5%)	5 (2.5%)
Median (IQR)	8 (4-17.5%)	6.5 (3-15.5)
Increase in CTSS	35 (17.5)%	**p<0.0001**

Table 4 : **Acute COVID infection and Post COVID sequelae**

Serial no.	Signs & Symtoms	On Admission	On Follow-up
1	Fever N (%) Median days	172 (86) 5 (1-10)	12 (6.0) 6 (2 - 8)
2	Fatigue N (%) Median (IQR)	170 (85) 4 (1-10)	151 (75.5) 12 (5 - 60)
3	Dyspnea Median (IQR)	184 (92) 4 (1-8)	140 (70) 14.5 (5 - 35)
4	Joint pain N (%) Median (IQR)	24 (12) 4 (2-7)	73 (36.5) 7 (4 - 30)
5	Chest pain N (%) Median (IQR)	54 (27) 3 (1-6)	37 (18.5) 7 (3 - 35)
6	Cough N (%) Median (IQR)	180 (90) 5 (1-8)	7 (3.5) 7 (7-15)
7	Rhinitis N (%) Median (IQR)	150 (75) 5 (1-7)	61 (30.5) 8 (5-25)
8	Sicca N (%) Median (IQR)	4 (2) 2 (1-4)	7 (3.5) 7 (7-15)
9	Anosmia N(%) Median (IQR)	76 (38) 10 (4-16)	111 (55.5) 8 (4 25)
10	Red eyes N (%) Median (IQR)	15 (7.5) 2 (1-4)	10 (5.0) 4.5 (4 15)
11	Dysgeusia N (%) Median (IQR)	90 (45) 7 (2-15)	87 (42.5) 8 (4 - 25)
12	Headache N (%) Median (IQR)	100 (50) 7 (2-12)	89 (44.5) 7 (4 - 21)
13	Anorexia N (%) Median (IQR)	80 (40) 4 (2-7)	57 (28.5) 8 (5 - 25)
14	Sore throat N (%) Median (IQR)	130 (65) 5 (1-7)	45 (22.5) 7 (4 - 9)

15	Vertigo N (%) Median (IQR)	8 (4) 2 (1-5)	38 (19.0) 5 (3 - 15)
16	Vascular N (%) Median (IQR)	10 (5) 5 (2-15)	2 (1.0) 4.5 (7 - 15)
17	Myalgia N (%) Median (IQR)	50 (25) 12 (2-20)	124 (62.0) 15 (4 - 30)
18	Diarrhea N (%) Median (IQR)	12 (4) 4 (3-6)	10 (5.0) 5 (2 - 8)
19	Rash N (%) Median (IQR)	0	4 (2.0) 7.5 (6 - 10)
20	Sleep Disorder N (%) Median (IQR)	0	23 (11.5) 7 (7 - 20)

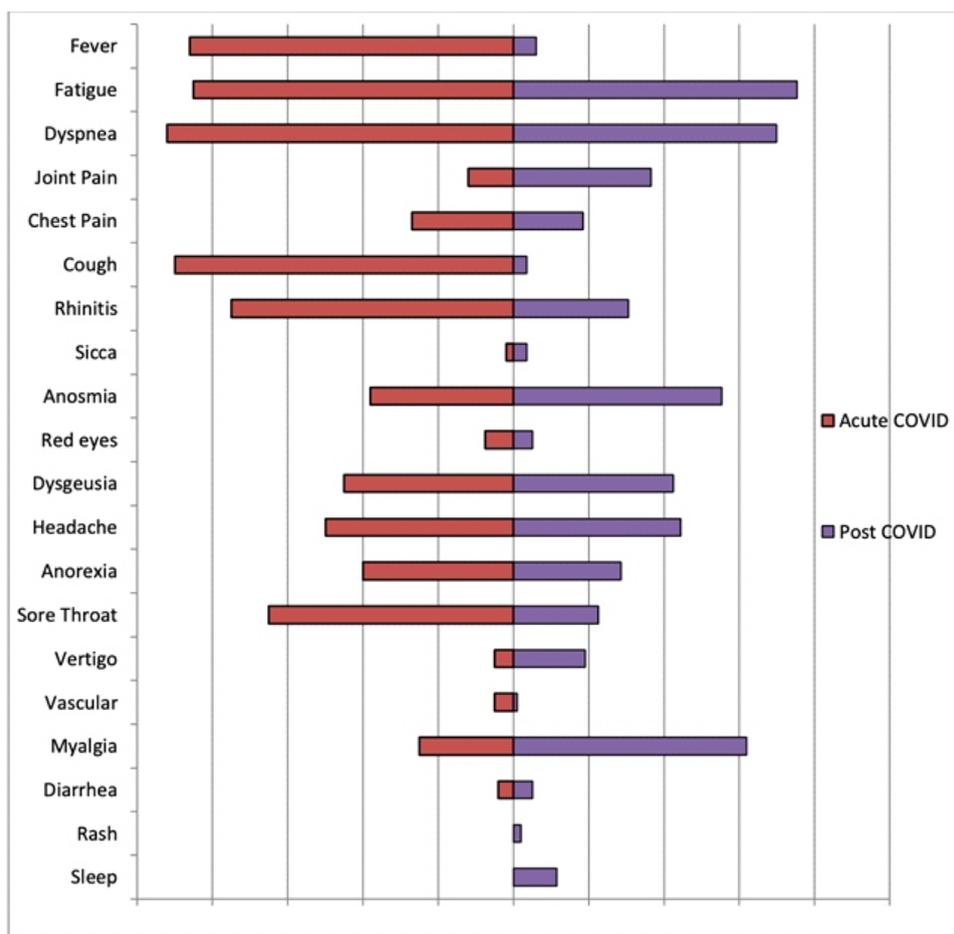**Fig. 2 : Acute COVID infection and Post COVID sequelae**
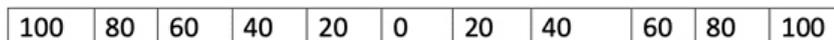
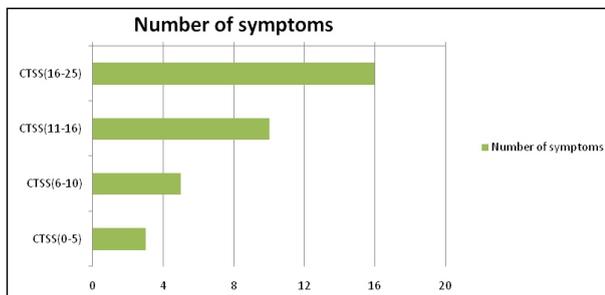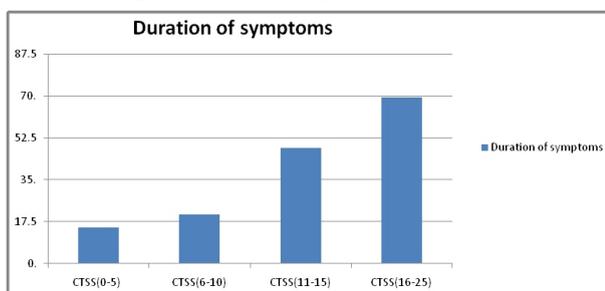*Fig. 3 :* **Co-relation of CTSS on admission and the number of symptoms on follow-up (Post COVID sequelae).**

Fig. 4 : **Co-relation of CTSS (on admission) and the duration of symptoms on follow-up (post COVID sequelae in days).**

Fig. 5 : **Median duration (days) of every symptom on discharge in post COVID 19 patients.**
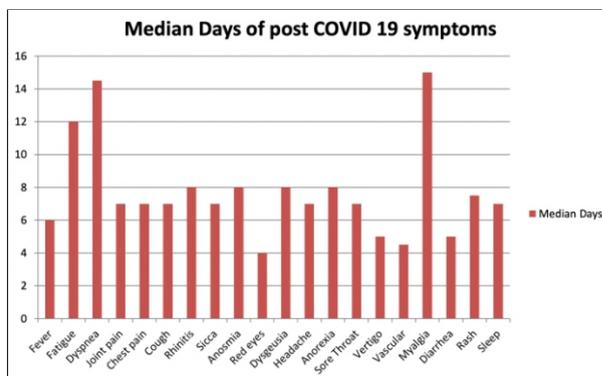
Fig. 5 : **Early and Late manifestations of COVID-19**

Discussion :

The coronavirus disease 2019 (COVID-19) pandemic has resulted in millions of patients infected worldwide and indirectly affecting even more individuals through disruption of daily living. From its first case in Wuhan, China in December 2019, to the first case in Kerala, India in January 2020; the infection has spread far and wide. A robust scientific and medical literature quickly emerged to provide information on patients vulnerable to the infection. Large scale preventive measures and treatment guidelines for the acute infection were formulated.

Emerging evidence suggests that COVID-19 adversely affects different systems in the human body.

Long-term outcomes have been reported with similar diseases from other coronaviruses, namely Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).

The scientific community and health care professionals are dealt with not only understanding the multifaceted ways in which COVID-19 affects the human body but also its long lasting effects . Even though the virus may not be actively replicating in the body, it shows effects that were not present prior to COVID-19 infection. These "Long-haulers" of COVID-19 have persistent symptoms well beyond the average course of recovery[1].

The COVID sequelae followup study done in Italy with 179 patients at a mean 60.3 days after onset of first COVID 19 symptom. It reported that only 18 % were completely free of sequelae. Fatigue (53.1%), dyspnea (43.4%) and chest pain (21.7%) were reported to be the most common symptoms and an overall decline in quality of life was observed in 44.1% of the patients.[2]

The long-haulers in CCS are new to the scientists and healthcare professionals, and it is expected to

take some time before the underlying pathogenesis of this condition gets resolved. Long haulers are considered to overlap with chronic fatigue syndrome. Factors like viral load, which may get eradicated or persist due to tissue binding may play a possible role in long haulers/chronic covid syndrome (CCS).[2] 'Long-COVID' or 'COVID long-haulers' generally describes those persons who experience symptoms for greater than 28 days after diagnosis, whether laboratory confirmed or clinical. [3,5]

Symptoms are as markedly heterogeneous as seen in acute COVID-19 and may be constant, fluctuate, or appear and be replaced by symptoms relating to other systems with varying frequency.[5]

A longitudinal follow-up study over 3 months was done in Wuhan, China with 538 covid survivors. The median age of patients was 52 years and time from discharge to follow-up was 97 days.

Similar to our study, it was found that 49.6% patients had persistent respiratory symptoms like cough and dyspnea on ordinary activity and 13% had cardiovascular symptoms like chest pain. There was significant association between acute COVID infection gravity and post discharge persistence in symptoms both in duration and severity.[6]

Major adverse outcomes were found to affect different body systems : including respiratory system (lung fibrosis and pulmonary thromboembolism), cardiovascular system (cardio-myopathy and coagulopathy), neurological system (sensory dysfunction & stroke), as well as cutaneous and gastrointestinal manifestations, impaired hepatic, renal function, immune system (including but not limited to Guillain-Barré syndrome and paediatric inflammatory multisystem syndrome).[4]

Since the virus mediates an immune response, weakens the immune system and causes inflammation, and genetically enters and lyses host cells and releases its genome into the cytoplasm, long term complications in patients surviving the COVID19 should be kept a close watch on.

Anticoagulant therapy in patients with high D-dimer levels or anti fibrosis medications like perfenidone or nintedanib are examples of therapeutic options for chronic covid syndrome.

Conclusion :

Two things that have been learned in the past 8-10 months with SARS-CoV-2 causing COVID-19 are (a) the more time we take to understand the pathogenesis and factors related to SARS-CoV-2 spread, causation of organ injury, and mutations occurring in its genome, the more SARS-CoV-2 has turned into a die-hard virus; (b) the delays that are occurring in understanding the pathogenesis and cascade of multiorgan involvement in acute and chronic-phases of SARS-CoV-2 infection are increasing the morbidity and mortality related to COVID-19.

A need to have a consensus on the duration after which the diagnosis of CCS in long-haulers can be proclaimed, which could prove to be of prognostic significance. Research in COVID-19 with data collection from long-haulers[4] in CCS are expected to uncover the molecular basis of the chronicity, with the identification of other novel pathways and mechanics that form the basis of long-haulers in CCS.

The burden of caring for COVID-19 survivors is likely to be huge. Therefore, it is important for policy makers to develop comprehensive strategies in providing resources and capacity in the healthcare system. Future epidemiological studies are needed to further investigate the long-term impact on COVID-19 survivors.

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