Original Article

An observational study on health-related quality of life and persistent symptoms in COVID-19 patients after hospitalization at a tertiary care centre

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ABSTRACT

Aim: The study aims to determine persistent symptoms and effects of COVID-19 infection on the quality of life (QOL) at 1 and 3 months after the acute phase of the disease in mild, moderate and severe cases. **Methods:** The prospective observational study was conducted among patients with confirmed COVID-19 who had been treated and discharged after hospitalization from February 2021 to June 2021. All patients were interviewed at 1 and 3 months post discharge to assess persisting symptoms and health-related QOL. QOL was assessed using European Quality Of Life 5-Dimensions 3-Levels (EQ-5D-3L) and EuroQol-visual analogue scales (EQ-VAS). **Results:** In total, 388 out of 479 discharged following COVID-19 infection were included. The median age of patients was 48 years, with 62.6% male predominance. Most of the COVID-19 cases were mild (67.01%). Most common presenting symptom was fever (69.8%). EQ-5D-3L showed that the problems reported at 3-month follow-up were significantly less when compared to 1-month follow-up ($p < 0.001$), and QOL significantly improved after 3 months in non-intensive care unit (ICU) patients when compared to ICU patients ($p = 0.007$). The mean EQ-VAS score significantly improved at 3 months when compared to 1 month (80.34 ± 12.77 vs. 91.69 ± 12.34; $P < 0.001$). The severity of illness was correlated with QOL ($p < 0.007$). **Conclusion:** The study results demonstrate ongoing improvement in the QOL and persistent symptoms, while a minority still were symptomatic after 3 months post-COVID-19 illness.

KEY WORDS: EQ-VAS, EQ-5D-3L, persistent symptoms, post COVID, quality of life (QOL)

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 in Wuhan, China. Within a few months thereafter, COVID-19 spread rapidly around the world and has now become a worldwide pandemic.[1-3] As of August 22, 2021, more than 211 million confirmed cases and more than 4 million people lost their lives due to SARS-CoV-2.[4] India has the second-highest number of confirmed COVID-19 positive cases in the world, after the United States, with more than 32 million reported cases of COVID-19 infection and more than 4.3 lakhs deaths as of 22 August 2021.[5] Hence, the main focus

Access this article online	
Quick Response Code:	**Website:** www.lungindia.com
	DOI: 10.4103/lungindia.lungindia_126_22

How to cite this article: Shah C, Keerthi BY, Gali JH. An observational study on health-related quality of life and persistent symptoms in COVID-19 patients after hospitalization at a tertiary care centre. Lung India 2023;40:12-8.

was to prevent, treat and develop vaccines for long-term immunity against COVID-19 infection.[6]

COVID-19 has several pulmonary and extrapulmonary manifestations.[7] Most of the patients have a favourable progression; however, few patients have worse outcomes, progressing to acute respiratory distress syndrome (ARDS) and requiring treatment in an intensive care unit (ICU). Persistent residual symptoms post COVID-19 infection came to wide attention after Centers for Disease Control and Prevention reported that people may experience symptoms for weeks to months even in mild disease.[8] Based on the duration of symptoms post infection, COVID-19 is divided into two categories: subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4 to 12 weeks beyond acute COVID-19, and chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19.[9]

Residual symptoms may be seen due to SARS-COV-2 viral infection, which have a significant association with duration of hospitalization, comorbidities and steroid use and abuse. Also, patients who survive may be susceptible to developing poor health-related quality of life (QOL) and persistent symptoms after ICU discharge; however, this has not been investigated.[10] Several studies have shown that health-related QOL has been significantly affected even in mild cases of COVID- 19.[11-13] However, there is very limited data on COVID-19 disease and persistent symptoms in the Indian population. For the first time in India, we aim to study persistent symptoms and effects of COVID-19 on QOL at 1 and 3 months after the acute phase of the disease in mild, moderate and severe cases. By far, the majority of COVID-19-related studies globally have been focused on transmission, infection, management and prevention. This study offers a different clinical perspective as it is one of the earliest and very few QOL-related COVID-19 studies conducted in India during the early pandemic. Additionally, the study also helps to focus beyond the limited scope of knowledge about post-COVID-19-affected quality of life.

MATERIALS AND METHODS

This prospective cross-sectional study evaluated all COVID-19 patients who were treated and discharged from our hospital between February 2021 and June 2021. The study was approved by the Institutional Scientific Research Committee. Ethics approval date SRC Number TIMS/2020-21/06 (Date 12/3/2021).

Informed consent was obtained from all the patients in their own native language before the initiation of the study. Patients who were above 18 years of age with a positive result on real-time reverse transcriptase-polymerase chain reaction or rapid antigen test on nasopharyngeal swabs were included. Patients having symptoms due to pre-existing underlying medical conditions 1 month prior to COVID-19 infection, deceased, transferred out or lost to follow-up were excluded from the study.

Documentation of all patients during hospitalization included demographic data, symptoms at the time of admission, day of illness (calculated from symptom onset) at admission, duration of hospital stay, comorbidities, maximum severity of disease attained during hospital stay (progression of the disease), need for oxygen support or higher mode of ventilation and its duration during hospitalization, steroid duration. Data was also collected for patients who were required to stay at the hospital for 1 month or more [Supplementary annexure 1]. Patients' severity at admission was divided into mild, moderate and severe categories according to the Indian Council of Medical Research grading. Mild severity was defined as upper respiratory tract symptoms with Spo2 >94 at room air; moderate severity as respiratory rate >24/min or Spo2 <94 at room air and severe as respiratory rate >30 min or Spo2 <90 at room air with pneumonia/ARDS/sepsis/septic shock.[14]

All patients were randomly selected, and every alternate case was included in the study as per the eligibility criteria. Open-ended questions were asked to assess persistent symptoms without any leading questions to avoid bias. All the patients were interviewed in their regional language by the physician. All eligible individuals were followed up via telephone calls at 1 month (first endpoint) and 3 months (second endpoint) after discharge.

The QOL of all study subjects was assessed using European Quality Of Life 5-Dimensions 3-Levels (EQ-5D-3L) and EuroQol-visual analogue scales (EQ-VAS).[15] The EQ-5D consists of five domains – mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has three levels and patients were asked to rate their health from 1 to 3, 1 indicating no problems at all, 2 indicating some problems and 3 indicating unable to perform activities, dress or wash oneself, unable to perform regular activities, extreme pain/discomfort and extremely anxious/depressed. Responses of all the five domains were merged, and EQ-5D-index was calculated, ranging from states worse than dead (<0) to 1 (full health).[16] The EQ-VAS records patients' self-rated health on a vertical VAS scale ranging from 0 (worst possible health) to 100 (best possible health) [Supplementary annexure 2 and 3].[16]

Statistical analysis

The data was analysed using R v. 3.3.1. The mean and percentages are presented as descriptive data. Pearson's Chi-squared test was applied to compare categorical variables, while paired *t*-test was applied to compare continuous variables. A comparison of the QOL in non-ICU and ICU patients at 1 and 3 months post-COVID-19 infection was done by employing a one-way ANOVA test. A paired *t*-test was employed to compare the QOL

in COVID-19-infected patients at 1 and 3 months post COVID-19 infection. Regression analysis was applied to identify parameters that had a significant effect on the QOL with the help of an empirical model. Confidence intervals were set at 95%, and a $P \leq 0.05$ was considered statistically significant.

RESULTS

Out of 479 patients screened, 91 were lost to follow-up and the analysis was done for 388 patients. Table 1 shows the baseline characteristics of patients hospitalized with COVID-19. The median age of patients was 48 years, with 62.6% male and 37.4% female patients. The majority of the patients had fever (69.8%) and cough (66%) at the time of admission. The most common comorbidity was hypertension (35%), followed by diabetes (29.38%), asthma (3.35%) and cardiac disease (3.09%). The mean length of stay in the hospital was 6.13 days, and in ICU was 1.34 days, while the oxygen required was for 6.21 days. Approximately within 16 days post discharge, patients resumed their professional or physical activities.

Table 2 shows the comparison of QOL in COVID-19-infected patients at 1 and 3 months post discharge. Patients reported moderate to extreme problems in the five dimensions, studied with the EQ-5D-3L at 3 months follow-up—mobility (82.8%), self-care (81.4%), usual activities (73%), pain/discomfort (49.8%) and anxiety/depression (82.4%)—were less compared to follow-up at 1 month. The mean EQ-VAS score was significantly improved at 3 months post COVID-19 infection when compared to 1 month ($P < 0.001$). QOL was significantly increased in non-ICU when compared to ICU patients at 3 months post COVID-19 infection ($p = 0.007$).

Out of 388 patients, 283 reported persistent symptoms at 1-month follow-up, while at 3-month follow-up, only 83 reported ongoing symptoms: 14.6% weakness, 2.57% body pains, 1.29% cough, 1.03% fever and 2.06% shortness of breath [Figure 1].Most of the symptoms improved at 3-month follow-up when compared to 1 month [Figure 1].
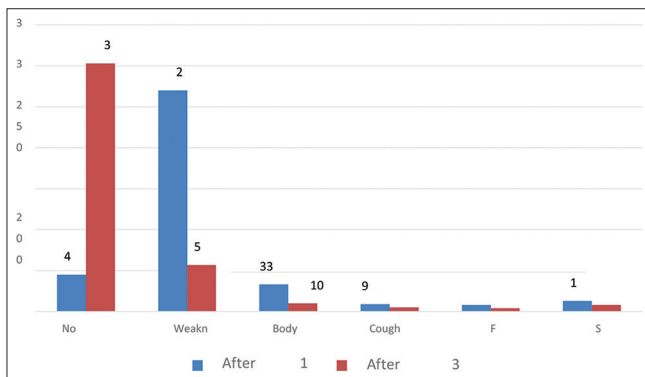

Figure 1: Symptoms persisting after 1 and 3 months. SOB – shortness of breath, F – fever

Figure 2 shows the health-related QOL at 1 and 3 months marked on a radar graph. Health-related QOL at 3 months was better than follow-up at 1 month.

Out of 388 COVID-19-infected patients, 260 (67.01%) were mild, 61 (15.72%) were moderate and 67 (17.26%) got admitted at a severe stage. Of the 260 mild cases, 194 (74.61%) had progressed from mild to the moderate stage and 4 (1.53%) patients progressed from mild to severe. Out of 61 moderate cases, 48 (78.69%) progressed from moderate to severe stage [Figure 3].

Table 1: Baseline characteristics of patients hospitalized with COVID-19

	n (%)
Demographics	
Age, median (IQR) [range], years	48, (36-59), [19-94]
Sex	
Female	145 (37.4)
Male	243 (62.6)
Steroid duration (range)	0-31
Symptoms at the time of admission	
Fever	271 (69.8)
Cough	256 (66)
Dyspnoea	193 (49.7)
Sore throat	61 (15.7)
Rhinorrhoea	65 (16.75)
Anosmia	48 (12.37)
Ageusia	48 (12.37)
Weakness	109 (28)
Myalgia	158 (40.7)
Chest pain	5 (1.3)
Loose motions	31 (7.98)
Vomiting	13 (3.35)
Headache	8 (2)
Haemoptysis	2 (0.5)
Admission data, Range, (Mean)	
Length of stay in hospital, days	1-28 (6.13)
Length of stay in ICU, days	0-28 (1.34)
Length of oxygen required, days	0-29 (6.21)
Day of illness at admission	(9.05)
Comorbidities	
Cardiovascular disease	
Hypertension	136 (35)
Diabetes	114 (3.09)
Cardiac disease	12 (3.09)
Deep vein thrombosis	1 (0.25)
Chronic respiratory disease	
Asthma	13 (3.35)
Tuberculosis (past history)	6 (1.34)
Inflammatory disease	
Rheumatoid arthritis	3 (0.7)
Osteoarthritis	1 (0.25)
Connective tissue disorder	1 (0.25)
Cancer	
Carcinoma cervix	1 (0.25)
Ovarian carcinoma	1 (0.25)
Benign prostatic hyperplasia	2 (0.5)
Cerebrovascular disease	4 (1)
Metabolic disease	
Obesity	10 (2.57)
Professional/physical activity	
Returned to work, days	15.9 (0.79)

ICU, intensive care unit; Results are expressed as count (%) for categorical variables and as mean (standard deviation) for quantitative variables.

Figure 4 shows the empirical model of factors affecting the QOL and persistent symptoms at 1 and 3 months post discharge after COVID-19 infection. Patient's age, gender, duration of steroid use, duration of hospital stay, duration of oxygen or ventilation required, comorbidities, day of illness at admission and severity at admission affected QOL at 1 and 3 months follow-up. Patients in elderly age group, male gender and patients with single or multiple comorbidities developed persisting symptoms after 1 and 3 months. The severity of admission was correlated with symptoms at admission and the day of illness at admission, which indicates that those who presented late to a hospital (beyond 7 days after symptom onset) had more symptoms and higher severity at the time of admission. It was noted that symptoms at admission neither affect the QOL nor have any association with persisting symptoms.

DISCUSSION

This is a one-of-a-kind study in India representing the health-related outcomes after 1 and 3 months post COVID-19 infection. We found that at 3-month follow-up, the most proportion of patients showed improvement in QOL and resolution of persistent symptoms compared to 1-month follow-up post COVID-19 infection.

In our study, most of the patients affected by COVID-19 infection were men (62.6%). Similarly, in a US community-based cohort study, men had a higher prevalence of COVID-19 infection with mild to moderate severity and a higher rate of hospitalization, which might be due to behaviour, exposure or intrinsic risk.[17] A prospective UK cohort study also showed the highest prevalence of COVID-19 infection in males (56%) with moderate severity of infection.[11] In contrast, studies conducted in China and Europe reported equal prevalence of COVID-19 infection in both men and women, with greater severity in men.[18-20]

Our study found that fever (69.8%), cough (66%), dyspnoea (49.7%) and myalgia (40.7%) were the most prevalent symptoms in COVID-19 patients and 14 patients were asymptomatic at the time of admission. The prospective UK-based cohort study reported that breathlessness (39%), fatigue (39%) and insomnia (24%) were the prevalent symptoms at the time of admission.[11]

Previous studies reported preexisting conditions including diabetes mellitus, hypertension, chronic respiratory disease and cardiovascular disease are potential risk factors for developing COVID-19- infection.[19,21] Also, preexisting comorbidities significantly lower the QOL in COVID-19 patients.[22,23] Similarly, in our study,

Table 2: Comparison of the quality of life in COVID-19-infected patients

Quality of life (EQ-5D-3L)	After 1 month	After 3 months	P
Characteristics			
Mobility			
No problems	39 (10.1)	66 (17.0)	<0.001
Some problems	202 (52.1)	150 (38.7)	
Unable to walk	146 (37.6)	171 (44.1)	
Self-care			
No problems	31 (8)	72 (18.6)	<0.001
Some problems	207 (53.4)	123 (31.7)	
Unable to wash or dress myself	150 (38.7)	193 (49.7)	
Usual activities			
No problems	26 (6.7)	66 (17)	0.002
Some problems	210 (54.1)	130 (33.5)	
Unable to perform	152 (39.2)	192 (49.5)	
Pain or discomfort			
No pain or discomfort	38 (9.8)	79 (20.4)	<0.001
Some pain or discomfort	195 (50.3)	114 (29.4)	
Extreme pain or discomfort	155 (39.9)	195 (50.3)	
Anxiety or depression			
Not anxious or depressed	27 (7)	68 (17.5)	<0.001
Moderately anxious or depressed	200 (51.5)	122 (31.4)	
Extremely anxious or depressed	161 (41.5)	198 (51)	
EQ-5D index	11.55 (3)	8.54 (2.62)	0.95
EQ-VAS (0-100)	80.34 (12.77)	91.69 (12.34)	<0.001
ICU vs. Non-ICU			0.007

Data was expressed as count (%) for categorical variables and as mean (standard deviation) for quantitative variables. *P*<0.05 is considered statistically significant. One-way ANOVA was applied to compare the severity of patients in ICU vs. non-ICU patients
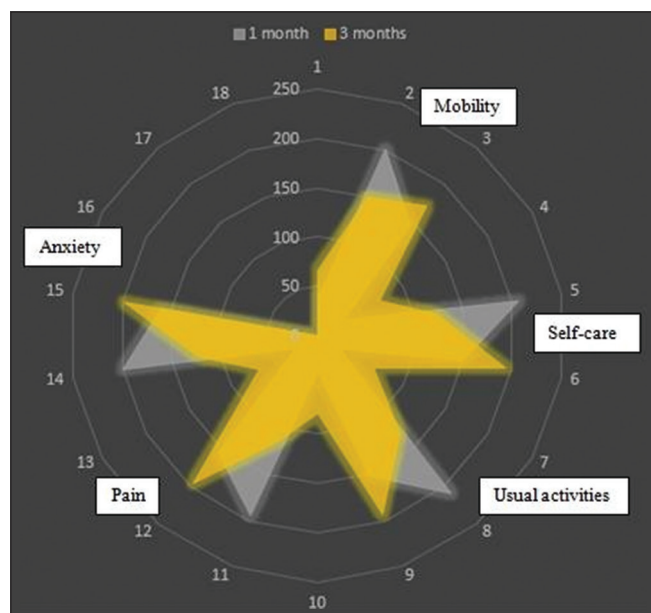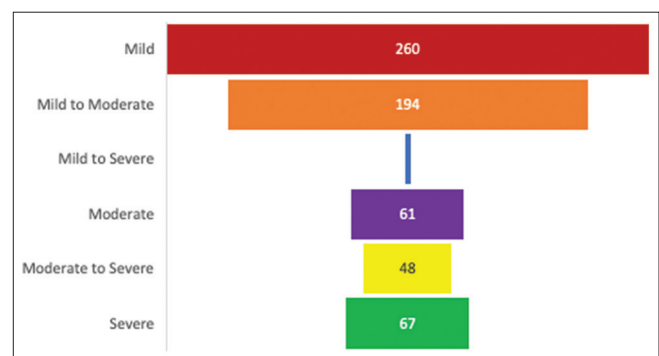

Figure 2: Health-related quality of life at 1 and 3 months

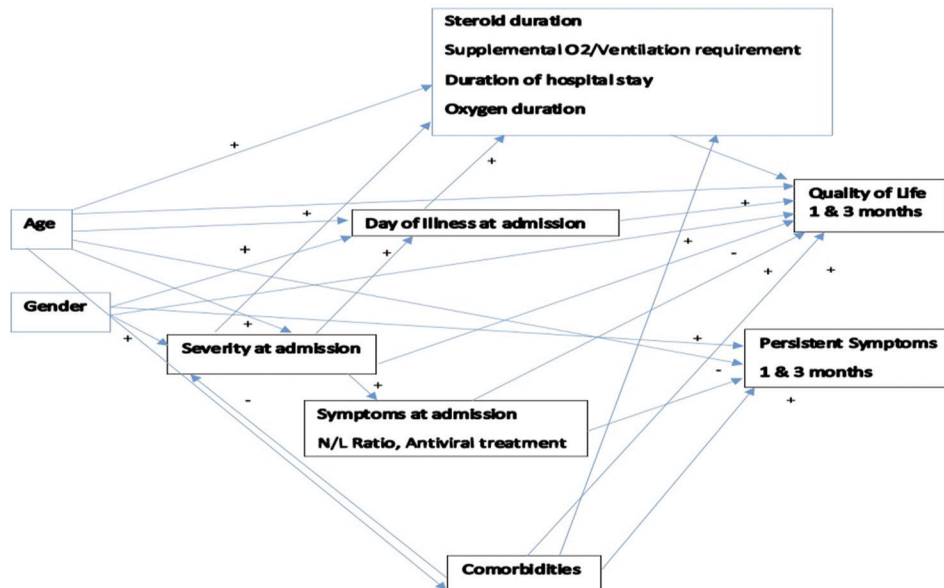
Figure 3: Progression of disease

Figure 4: Empirical model of factors affecting the quality of life and persistent symptoms at 1 and 3 months post discharge after COVID-19 infection

hypertension (35%) and diabetes (29.38%) were the most common comorbidities observed in COVID-19 patients, indicating that these patients are more prone to be critically ill after hospitalization. Furthermore, in our study, comorbidity was an important determinant for QOL and persistent symptoms.

The mean length of hospital stay was found to be 6 days. In a study conducted by Carfì *et al*.[20], the mean duration of hospital stay was 13 days. The difference in findings from our study might be due to different racial or ethnic composition or severity of the disease. Most of the COVID-19-infected patients presented with mild severity (81%). Similarly, Augustin *et al*.[13] reported 97.1% of patients (930/958) presented with mild disease (score 1–3) in accordance with the WHO COVID-19 clinical progression scale. In our study, most of the patients resumed work within 15 days post COVID-19 infection indicating satisfactory health-related outcomes.

In this study, weakness (69.5%) and body pains (8.5%) were the most common persisting symptoms after 1-month follow-up. Although there was recovery after 3 months, a minority still were symptomatic. In developing countries, this poses an economic challenge to the individual and society for the extended cost of care. Hence, research is needed to understand long-term effects of COVID 19.

The US-based prospective cohort study reported fatigue (55.0%) and dyspnoea (45.3%) accompanied by some or much difficulty with walking (15.6%), lifting and carrying (25.5%), walking upstairs (29.9%) and walking fast (45.6%) were the persistent symptoms, which significantly impacted patients' general, physical and mental health status, social functioning and QOL within 35 days of discharge.[3] The Italian study undertaken at 60 days post discharge found fatigue, dyspnoea, joint pain and chest pain were the most prevalent symptoms.[20] Other prospective studies also stated that fatigue, dyspnoea and hair loss were the most common symptoms in hospitalized COVID-19 patients even 110 days after discharge.[24,25] Interestingly enough, in our study, we found that 14 patients were asymptomatic at the time of admission, and yet they had persisting symptoms at 1-month follow-up. Two out of these 14 patients had symptoms persisting after 3 months as well.

In our study, health-related QOL at 3 months was better when compared to 1 month with respect to mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In a 6-month follow-up study, 61/91 COVID survivors showed a decrease in the QOL, and most of the patients reported moderate to extreme problems in the five dimensions on the EQ-5D-3L scale (mobility [56%], usual activities [37%], self-care [13%], pain/discomfort [48%] and anxiety/depression [46%]) when compared to before COVD-19 infection.[10] The study also showed significantly lower EQ-5D index and EQ-VAS score both before COVID-19 infection and a 6-month follow-up period.[10] We found a significant difference in the QOL for non-ICU and ICU patients at 3-month post COVID-19 infection, indicating that QOL in ICU cases deteriorated more/had a larger effect as compared to the non-ICU group. In contrast, Garrigues *et al*.[24] reported a mean EQ-VAS of 70.3% and a mean EQ-5D index of 0.86, without any significant difference between ICU and ward patients.

Our study underlines that age, gender, steroid duration, duration of hospital stay, oxygen requirement or ventilation support and its duration, comorbidities, day of illness at admission severity at admission are the most significant factors affecting QOL post COVID-19 infection. Quite

similar to our study, prior studies reported that advanced age, gender, need for mechanical ventilation during ICU stay, ARDS, duration of mechanical ventilation, length of ICU stay and length of hospital stay were the significant determinants of QOL in COVID patients.[10,26] In another study, it was also found that female sex, early symptoms (>5), early dyspnoea, anosmia, diarrhoea and prior psychiatric disorders during COVID-19 were associated with a higher risk of developing long-term symptoms.[13,27] Similarly, in our study, age, gender of the patients and comorbidities were the factors involved in the development of persistent symptoms in COVID-19-infected patients at 1 and 3 months follow-up. Furthermore, the QOL of COVID-19-infected patients who reported late to the hospital was affected more severely as compared to those presenting early. This is because those who reported late to the hospital had a more severe form of disease, leading to a longer hospital stay, steroid usage and oxygen requirement.

Limitations
Alike other studies, the present study has few potential limitations that need to be acknowledged. First, longer follow-up studies in a larger population are necessary to comprehend the full spectrum of health consequences from COVID-19 to plan proper rehabilitation programs. Second, single-centre nature of our study and the high rate of inaccessible patients might limit the generalization of the study results. Third, QOL before COVID-19 infection might impact the findings after 1 and 3 months post COVID-19 infection.

CONCLUSION

Our study demonstrates improved QOL and symptoms, more so in mild disease and with early diagnosis and treatment. Age, comorbidities and severe disease correlate with longer symptoms and reduced QOL. Thus, COVID-19 infection continues to challenge countries, especially developing, with ongoing burden, cost of care and reduced overall productivity. Therefore, there is a need to identify, research and cater to the long-term effects of post- COVID persistent symptoms.

Acknowledgments
We would like to thank all the patients who consented to share their data for analysis. We thank Dr. Vini Mehta, STAT SENSE for critical suggestions and statistical analysis. We have adopted the EQ-5D questionnaire by EuroQol Research Foundation for this study and are thankful to them for their permission.

Declaration of patients' consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed [Supplementary annexure 4].

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary annexure 1

PROFORMA

1. NAME OF PATIENT
2. AGE
3. GENDER
4. BMI
5. DATE OF ADMISSION/LENGTH OF HOSPITAL STAY
6. DURATION OF ILLNESS AT TIME OF ADMISSION
7. SEVERITY GRADING (ICMR GRADING)
8. CO-MORBIDITIES – DM, HTN, CARDIOVASCULAR DISEASES, CEREBROVASCULAR DISEASES, RESPIRATORY CONDITIONS, RENAL CONDITIONS
9. ADDICTIONS – SMOKING, ALCOHOL
10. SYMPTOMS AT TIME OF ADMISSION
11. SYMPTOMS PERSISTING IF ANY AT FIRST AND SECOND END POINTS
12. DAY OF OXYGEN REQUIREMENT (SINCE ONSET OF SYMPTOMS)
13. DURATION OF OXYGEN REQUIREMENT
14. HABITS/ADDICTIONS
15. MODE OF VENTILATION USED – NON-INVASIVE/INVASIVE/BOTH
16. HOME OXYGEN REQUIREMENT AT DISCHARGE
17. DEATHS AFTER DISCHARGE
18. EXERCISE AND PULMONARY REHABILITATION REQUIREMENT AFTER DISCHARGE
19. WAS PATIENT WORKING PRE-COVID
20. NUMBER OF DAYS TAKEN TO RESUME WORK POST RECOVERY

Supplementary annexure 2 and 3

Appendix: The EQ-5D instrument

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*eg work, study, housework, family or leisure activities*)
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

Pain/Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Note: The actual EQ-5D instrument spreads over two pages with the "thermometer" and explanation on page 2. To save journal space in this paper it has been compressed into on

Your own health state today

Best imaginabl health st;
100
9 0
8 0
7 0
6 0
5 0
4 0
3 0
2 0
1 0
0
Worst imaginabl health st;

EuroQol Group. EuroQolda new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199e208.[9]

Brooks R, with the EuroQol Group (1996) EuroQol: the current state of play. Health Policy **37**:53–72.[10]

CONSENT FORM
Title of the project:

Participant's name: Address:

The details of the study have been provided to me in writing and explained to me in my own language. I confirm that I have understood the above study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the above study.

(I also consent/do not consent to use my stored biological samples for future scientific purposes: Yes/No – if applicable)

Signature of the participant: _____ Date: _____

Signature of the witness: _____ Date: _____

Name and address of the witness:

Signature of the investigator: _____ Date: _____