



Case Study on Post-Discharge Persistence or Reappearance of Respiratory Symptoms in COVID-19 Hypoxia Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: News published about persistence or reappearance of symptoms in Covid 19 is worrisome. However, only one study from Italy is observed in this reference.

Aim: the current study is conducted to study persistence or reappearance of especially respiratory symptoms amongst COVID 19 hypoxia patients.

Study Design: Post-discharge follow-up, observational study with the telephonic interview of Covid 19 hypoxia patients from a dedicated Covid 19 hospital in India.

Methods: Sixty-two patients were interviewed 1 – 3 months post-discharge to elicit history on persistence or reappearance of respiratory symptoms.

Results: out of the results many patients doesnot show any symptoms compared to female, male are more prone to respiratory problems. Thus, the oxygen therapy showed proof that males are

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more prone to illness and depict the symptoms compared to females.

Conclusion: A large multi-centric year-long study is recommended to further conclude on the natural history of the disease.

Keywords: Persistence; respiratory; symptoms; COVID19; post discharge; hypoxia; dyspnea.

1. INTRODUCTION

Coronavirus has caused a pandemic and has affected 213 countries all over the world. India has total cases of 2,589,208, with 63,986 newly diagnosed cases on 15th August 2020 [1]. The pandemic has exhausted the healthcare system like never before all over the world. Also, it has caused a substantial loss in the world economy.

The United States of America (USA) shares 22.7% of total infection cases, followed by India and Brazil, sharing 13.5% and 9.6% of cases, respectively. Although a decrease in death rate is observed (September 10, 3.22; July 20, 6.65%; April 10, 22.36% and Feb 2, 41.80%), there is no substantial reduction in active COVID-19 cases (>700,000- daily cases on December 19, 2020) [2]. The cumulative incidences for COVID-19 vary by a multitude of factors, including comorbidities, age, gender, health and living conditions [3].

COVID 19 is primarily observed as the respiratory system's disease leading to severe acute respiratory symptoms and pneumonia. Symptoms like cough, cold, breathlessness, fever, severe myalgia, anosmia, and diarrhea/ GI symptoms are present in COVID 19 patients [4]. The disease has an incubation period of two to fourteen days. The approximate time to develop symptoms is five days, and to develop pneumonia is nine days. Not all the infected patients develop symptoms; some patients do not develop symptoms and act as silent carriers of the disease [5]. In India, it is observed that 82 % of COVID 19 patients had mild or a typical illness, 15% had moderate to severe illness, 3% had critical illness, and 2.3 % patients died [6]. Low Oxygen saturation or hypoxia means oxygen saturation less than 95% on room air [7]. Hypoxia is an utmost important symptom in COVID 19 patients because it may lead to critical illness patients [8].

The news articles that floated on 11 July 2020 about research are published in the 'Journal of the American Medical Association (JAMA)'. The study reported that around 87.4 % of COVID 19 patients in Italy reported persistently minimum one symptom, mostly fatigue and dyspnoea,

even discharged from the hospital after two months. This study prompted the present study focussing on respiratory symptoms in patients with hypoxia [9].

The present study will help to understand the natural history of the disease in COVID 19 patients with hypoxia post-discharge from the hospital [10].

2. OBJECTIVE

To study persistence or reappearance of respiratory symptoms amongst COVID 19 patients with hypoxia

3. REVIEW OF LITERATURE

The origin of corona virus was started initially a decade before where a common cold was one of the common factors. As years pass by the strain starts to mutate itself and with 7 different strains arose among which 3 different strains proved to fatal and causes alarming situation to humans from bats. Among that SARS-CoV, MERS-CoV and COVID-19 is an animal virus spreads to humans by an intermediate hosts. The pandemic situation arise a global challenge where the origin was from the Wuhan, in People's Republic of China causing a serious viral pneumonia in more than 213 countries across the world and WHO declared as global pandemic [10].

The infection was considered as natural virus of animal origin with severe infection potential [11] and it was started in the market of China but the source was unknown initially later it was considered the disease has been spread from bats and later on from pangolins [12]. International Committee on Taxonomy of Viruses (ICTV) announced SARS-CoV2 as the name of the new virus on February 11, 2020, because of the genetic resemblance of the virus to the CoV responsible for the outbreak of 2003. Following guiding principles previously developed with the World Organization for Animal Health (OIE) and the Food and Agriculture Organization (FAO) of the United Nations, WHO named the disease "COVID-19" and announced it as a global pandemic on March 11, 2020.

The hypoxia is a term used to refer shortness of breath where the virus affects the blood vessels and the airways. In addition to this the virus also infects the nervous system and affects the brain nerve which is responsible to regulate the respiration rate. The reason behind the lowering of oxygen refers to the blood flow in lungs reduced followed by the airflow in the lungs where the air sacs gets blocked which leads to the drop of oxygen level. But in some cases the initial symptom of shortness of breath is not been present in spite of person being infected. The virus infects the brain nerve where the blood vessels lack to mediate and the response from the brain signal inhibits the flow of blood supply which leads to hypoxia. The main reaction happens in the scenario is that the oxygen level is not dropping in the lungs but whereas the concern of the organs in the body is not getting enough oxygen they require to perform an action.

4. MATERIALS AND METHODS

4.1 Study Design

Present study is a follow-up observational study conducted at a Dedicated COVID 19 Hospital in India.

4.2 Sample

All patients above 18 years of age who were required to be given oxygen during their stay in the hospital were selected for the study. The first COVID 19 positive patient was admitted to the hospital on 9th April 2020. The study aims to have a follow-up for persistence or reappearance of symptoms between 1 – 3 months post-discharge from the hospital. Hence, patients discharged between 9th April and 31st July 2020, were selected in the study.

4.3 Case Definition

COVID 19 patients must be given oxygen during their stay in hospital due to hypoxia defined as oxygen saturation less than 95% on room air measured with the Covidien Nellcor Bedside pulse oximeter [11]. All the patients were routinely monitored for oxygen saturation every eight hourly in the wards.

5. DATA COLLECTION

The various primary and secondary data are used for the study,

5.1 Primary Data

Telephonic interviews were conducted to collect information on persistence or reappearance of respiratory symptoms viz. cough, cold, fever, chest pain, Breathlessness or Breathlessness on exertion, body ache/myalgia, and any other symptom patients want to report.

All investigators did the data collection with the standardized process of tele-interview [12] with following steps: a) initial greetings from the hospital; b) introduction of the investigator; c) inquiry about overall health; d) information about why study being conducted – to understand the natural history of the disease as it is a novel disease; e) informed verbal consent; f) if willing, then questions related to persistence or reappearance of respiratory symptoms, and presence of co-morbidity; g) thanking the respondent, h) addressing queries of the respondent, if any; and i) reassurance of any assistance required in future from the hospital.

5.2 Secondary Data

The demographics data and clinical characteristics were collected from the hospital's electronic case records.

5.3 Study Period

The study was planned to be conducted over two months, starting the data collection from 1st July 2020, and data collection was continued until 23rd August 2020, as some patients responded to pick their phones later after repeated calls. Patients who did not pick up the phone despite contacting for a minimum of six times over one and half months were then not further contacted.

6. RESULTS AND DISCUSSION

Total 501 COVID 19 patients were discharged between 9th April and 31st May 2020 from the hospital, and of these, 57 patients were below 18 years of age. Of the remaining 444 patients (Males = 241, Females = 203) who were above 18 years of age, 91 patients (Male = 59, Female = 32) were given oxygen therapy due to occurrence of hypoxia, during their stay in the hospital.

Out of the 91 patients given oxygen therapy, 14 patients died during the treatment (15.4% of those required oxygen therapy while 2.8% of the overall discharged patients).

Thus, 77 patients given oxygen therapy were selected in the study for persistence or reappearance of respiratory symptoms. Of these 77 patients, 12 patients could not be contacted telephonically due to invalid mobile numbers, and three patients did not pick up the phone despite calling them six times throughout one and a half months.

Therefore, total 62 COVID 19 patients given oxygen therapy during hospital stay could be contacted for eliciting history for persistence or reappearance of respiratory symptoms 1 – 3 months post-discharge from the COVID 19 Dedicated hospital.

6.1 Demographic Characteristics of the Study Sample

Section describes the distribution of the study sample according to age and sex.

Fig. 1 shows that the male to female ratio of patients requiring oxygen is 1:0.6 patients, with

39 patients (62.9%) being males and 23 patients (37.1%) females. It is further observed that more males required oxygen in the age group of 40 – 60 years (24/39 – 61.5%), while in females, more number required oxygen in the age group of 60 – 80 years (15/23 – 65.2%).

Table 1 shows that the study sample's overall mean age is 57.3 years (Minimum = 26, Maximum = 80), with the mean age of Males as 53.5 years and that of Females was 63.7 years. This difference is statistically significant using Independent Sample 't' test (t value = -3.075, df = 60, p < 0.01). Table 2 shows the Levene's Test for these independent samples.

6.2 Clinical Characteristics of the Study Sample

Section describes the presence of co-morbidities and duration of oxygen therapy in the study sample.

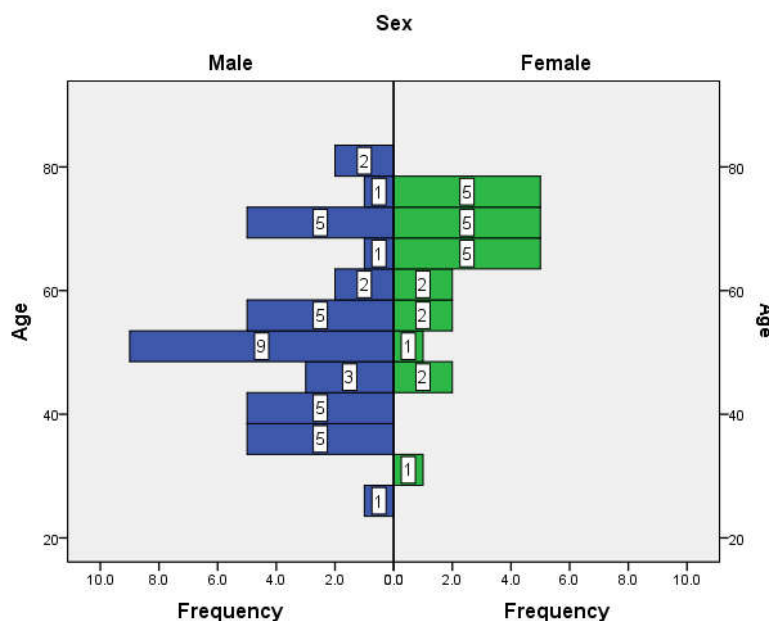


Fig. 1. The distribution of study sample according to age and sex (N = 62)

Table 1. Comparison of mean age of study sample according to sex (N = 62)

	Sex	N	Mean	SD	SE mean
Age	Male	39	53.5	13.300	2.130
	Female	23	63.7	11.343	2.365
	Total	62	57.3	13.464	1.710

SD: Standard Deviation, SE: Standard Error of Mean

6.3 Presence of Co-Morbidities in the Study Sample

RA – Rheumatoid Arthritis, COPD – Chronic obstructive pulmonary disease, DM – Diabetes Mellitus, HTN – Hypertension. Fig. 2 shows that of the 62 patients, 41.9% have HTN, 30.6% have DM, 9.7% have COPD, and 6.4% have Cardiac problems and one case of RA and Hypothyroidism.

6.4 Mean Duration of Oxygen Therapy in the Study Sample

Table 3 shows that the overall mean duration of oxygen therapy in the study sample is 6.7 days (Minimum = 0.5 days, Maximum = 19 days). The Mean duration of oxygen therapy in males is 6.2

days, and in females, it is 7.7 days. This difference is not statistically significant. The Levene's Test for independent samples for several days' oxygen's given is shown in Table 4.

6.5 Post-Discharge Mean Period of Follow up With a Telephonic Interview

Table 5 shows that the overall post-discharge mean period follow-up is 65.7 days (Minimum = 50 days, Maximum = 88 days). The post-discharge mean period of follow-up in males is 64.4 days, and in females, it is 68.0 days. This difference is not statistically significant. Table 6 shows Levene's Test of independent samples for the post-discharge mean period follow.

Table 2. Levene's test of independent samples for ages

		Levene's Test		Independent Sample 'to test				
		F value	p-value	t value	Df	p-value	Mean Difference	SE Difference
Age	Equal variances	1.071	.305	-	60	.003	-10.201	3.317
	No equal variances			3.075	52.252	.002	-10.201	3.183

Table 3. Comparison of the mean duration of oxygen therapy according to sex (N = 62)

	Sex	N	Mean	SD	SE means
Number of days oxygen given	Male	38	6.2	5.243	.851
	Female	23	7.7	4.809	1.003
	Total	62	6.7	5.099	0.653

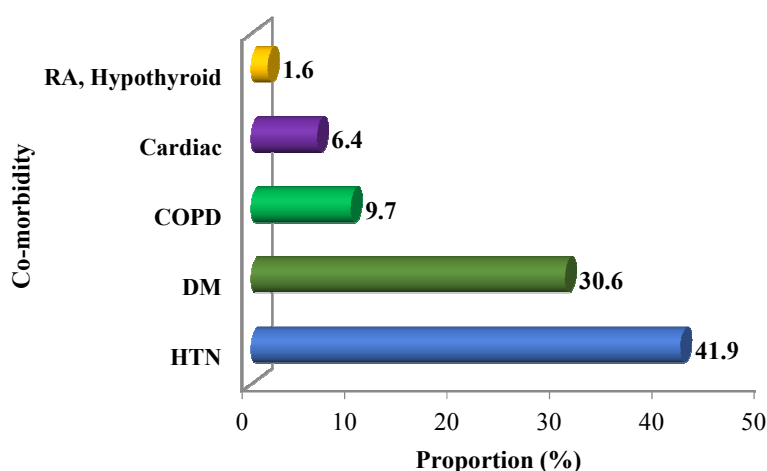


Fig. 2. Proportion of study sample with co-morbidities (N = 62)

Table 4. Levene’s test of independent samples for several days’ oxygen’s given

		Levene's Test		Independent Sample 'to test				
		F value	p-value	t value	df	p-value	Mean Difference	SE Difference
Number of days oxygen given	Equal variances	.734	.395	-1.145	60	.257	-1.538	1.344
	No equal variances			-1.169	52.252	.248	-1.538	1.315

Table 5. Comparison of a post-discharge mean period of follow up according to sex (N = 62)

	Sex	N	Mean	SD	SE means
The post-discharge mean period of follow up	Male	39	64.4	10.336	1.655
	Female	23	68.0	9.858	2.056
	Total	62	65.7	10.230	1.299

Table 6. Levene's Test of independent samples for the post-discharge mean period follow up

		Levene's Test		Independent Sample 'to test				
		F value	p-value	t value	df	p-value	Mean Difference	SE Difference
The post-discharge mean period of follow up	Equal variances	.034	.854	-1.343	60	.184	-3.590	2.672
	No equal variances			-1.360	48.073	.180	-3.590	2.639

6.6 Persistence or Reappearance of Symptoms

Only ten patients out of 62 (16.1%) reported reappearance of symptoms viz. 4 patients with Cough (duration ranging from 2 – 7 days), two patients with Cold or Running nose (duration 2 – 3 days), 1 case with fever for duration three days and three patients of breathlessness. Out of the three patients reporting breathlessness, one case had breathlessness for seven days after discharge and then got completely better, one known COPD case with occasional bouts of breathlessness. One case has continued Grade II Dyspnea, which he never had before COVID 19. 83.9% of patients have no respiratory symptoms of cough, cold, fever, or breathlessness. No one reported Chest pain or any other COVID-related symptoms except for weakness which two patients reported. Thus, post-discharge, from Fig. 3, only one patient has persistent clinically significant Grade II Dyspnea related to COVID 19. This case is a 53-year-old male patient with post-discharge follow up on the 66th day.

6.7 Profile of Patients Reporting Persistence or Reappearance of Symptoms

There are six males and four females who reported persistence or reappearance of symptoms. The mean age of these patients is 58.7 years. Of them, two patients have Hypertension, and two patients have Diabetes mellitus. The mean duration of oxygen therapy given to these patients is 5.2 days.

Table 7 shows no statistically significant difference between the mean age of cases with and without persistent or reappearance of symptoms.

Table 8 shows a statistically significant difference between the mean duration of oxygen therapy in patients with and without persistent or reappearance of symptoms. However, the mean duration is lower in patients with persistent or reappearance of symptoms which is paradoxical.

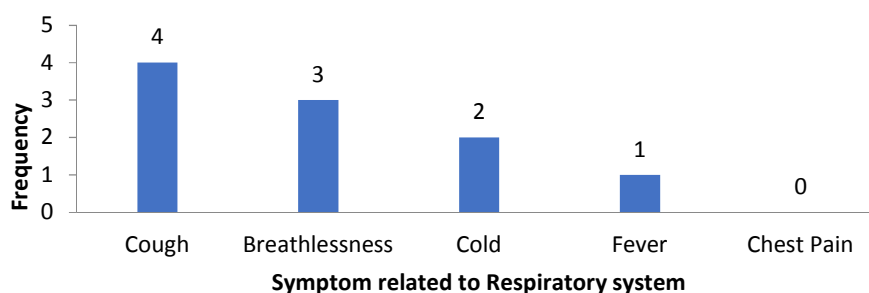


Fig. 3. Persistence or reappearance of symptoms related to respiratory system 1–3 months post-discharge in patients given oxygen therapy during the stay in hospital (N = 10)

Table 7. Comparison of the mean age in patients with and without persistent or reappearance of symptoms (N = 62)

Post-discharge symptoms	N	Mean	SD	SE Mean	't' test
No	52	57.1	14.003	1.942	t = -.351 df= 60 P > 0.05
Yes	10	58.7	10.719	3.390	

Table 8. Comparison of the mean duration of oxygen therapy in cases with and without persistent or reappearance of symptoms (N = 62)

Post-discharge symptoms	N	Mean	SD	SE Mean	't' test
No	52	7.0	5.188	.727	t = 1.044 df = 60 P > 0.05
Yes	10	5.2	4.541	1.436	

7. DISCUSSION

The study is prompted since there is plenty of news on the internet regarding the reappearance or persistence of symptoms regarding COVID-19 cases.

News in Economic times dated Feb 28, 2020, mentions a growing number of cases coming positive after recovery in China and elsewhere. A woman in Japan also tested positive a second time [11]. Daji world media network reported in the headlines of the news dated Wed, Apr 15, 2020, that reappearance of symptoms are seen in COVID 19 patients in Udupi; however, these were cases that had prolonged COVID test positive [12].

Dominic Hughes, health correspondent BBC News reported on May 19, 2020 about a 42-year-old case from Bristol, England having reappearance of symptoms [13]. A news article dated May 23, 2020 in 'Web 24 news' gives a headline that symptoms are reappearing in COVID-19 patients [14]. Ed Yong's story in 'The Atlantic Daily,' dated June 4, 2020 describes a journalist who was experiencing symptoms even on Day 66 [15].

Consequently, only one study was published on July 9, 2020, from Italy, in which 143 patients were assessed after a mean of 60.3 days after the appearance of the first COVID-19 symptom. The average age of these cases in the study was 56.5 years. It was observed that there was no COVID-19 related symptom in 12.6%, one or two symptoms in 32 %, and three or more symptoms in 55% of study participants. No patients had symptoms of acute illness or fever, or any other signs [10].

Mumbai mirror and other newspapers in India reported on August 4, 2020 that 22 patients recovered from COVID 19 returned with pulmonary fibrosis at KEM Hospital Mumbai, India [16]. The present study focuses on the persistence or reappearance of specifically respiratory symptoms in COVID 19 patients with hypoxia and oxygen therapy during their stay in the hospital. The mean age of our patients is 57.3 years, similar to the Italy study. The findings contrast that only one patient out of 62 cases has dyspnoea reported on the 68th-day post-discharge from the hospital. CNN News 18 has reported on August 11, 2020 that ICMR with 15 centres is preparing for data on the recovered

cases for any reappearance or persistence of worrying symptoms [17].

8. CONCLUSIONS

Post-discharge, only one patient has persistent clinically significant Grade II Dyspnea related to COVID 19. Otherwise, all patients given oxygen therapy while admitted in the hospital have no persistence or reappearance of respiratory symptoms for 1 – 3 months post-discharge. More males require oxygen therapy in COVID 19 as compared to females. Amongst females, oxygen therapy is required more in older females above 60 years of age. Thus, there will be few cases that may have persistence or reappearance of symptoms. The proportion of the case profile will have persistence or reappearance of symptoms. It is This novel disease needs such studies that are important to understand the natural history of the disease. ICMR with 15 centres is preparing for data on the recovered cases for any reappearance or persistence of worrying symptoms.

FUTURE SCOPE

It is to recommend that a larger multi-centric study can be conducted with a once-in-month follow-up of cases for one year and based on the obtained results various statistical datas can be added using SPSS software version 20.

ETHICAL CLEARANCE

Approved by IEC committee, Symbiosis International (Deemed University)

CONSENT

An informed verbal consent was taken from all patients.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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