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Predictors of pulmonary manifestations in long -COVID

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Abstract

Background and objective: Very limited data is available in India regarding the predictors leading to the development of pulmonary manifestations in long- COVID. The objective of this study was to identify the factors leading to the development of pulmonary manifestations, namely persistent cough and dyspnea in long -COVID.

Methodology: Retrospective analysis of medical records of all COVID 19 infected patients attending the Pulmonary Medicine outpatient department in PRS Hospital from November 2020 to July 2021 over a period of 9 months were utilized for the study. Those adult patients with persistent cough and/or breathing difficulty for more than 12 weeks after positive COVID 19 tests were included in the analysis.

Results: Five hundred and four patients were included in the study. The mean age was 49.9 ± 16.8. Males constituted the majority with 53.6 %(N=270) compared to females (46.4%, N=234)]. More than 5 symptoms which include fever, loss of smell, loss of taste, cough, breathlessness, hemoptysis, diarrhea, fatigue and headache were present in 28.2 %(N=142) individuals. Patients who had long- COVID pulmonary symptoms were more (N=308, 61.1%) than those who had no long- COVID pulmonary symptoms (N=196, 38.9%). Patients with more than 60 years of age and of male gender with presence of comorbidities, rising titer of inflammatory markers within the first 2 weeks of illness, presence of parenchymal bands on CT scan and those who required home oxygen therapy following hospitalization were associated with long- COVID pulmonary symptoms.

Conclusions: Early identification of risk factors might help in preventing long term complications like pulmonary fibrosis

Keywords: Long- COVID; Pulmonary; Cough; Dyspnoea; Predictors

1. Introduction

"Long- COVID" is a term used to describe the presence of various symptoms, even weeks or months after acquiring SARS-CoV-2 infection irrespective of the viral status. It is also called "post-COVID syndrome". It can be continuous or relapsing and remitting in nature. There can be the persistence of one or more symptoms of acute COVID, or appearance of new symptoms. Majority of people with post COVID syndrome are PCR negative, which indicates microbiological recovery. In other words, post COVID syndrome is the time lag between the microbiological recovery and clinical recovery. Majority of those with long -COVID show biochemical and radiological recovery. Depending upon the duration of symptoms, post COVID or long -COVID can be divided into two stages-post acute COVID where symptoms extend beyond 3 weeks, but less than 12 weeks, and chronic COVID where symptoms extend beyond 12 weeks [1]. Long -COVID can be summarized as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection along with these symptoms lasting for at least 2 months with no other explanation. The term long- COVID is used to describe signs and symptoms that continue or develop after acute COVID-19 infection. It includes both ongoing

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symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Long- COVID is the collective term to denote the persistence of symptoms in those who have recovered from SARS-CoV-2 infection. The pandemic of COVID-19 is the biggest public health crisis in the twenty first Century. In addition to the acute symptoms after COVID -19 infection, patients and society are also being challenged by the long-term health complications associated with COVID-19, commonly known as long -COVID. The lingering symptoms after COVID-19 infection can last weeks to months. These symptoms severely reduce the quality of life long after patients become virus-free [2].

Objectives

The objective of this study was to identify the factors leading to the development of pulmonary manifestations, namely persistent cough and dyspnoea in long -COVID.

2. Materials and methods

This was a retrospective analysis done in Pulmonary Medicine department In PRS Hospital, Trivandrum, Kerala. The medical records of all patients with documented COVID 19 positive results who attended the Pulmonary Medicine outpatient department from November 2020 to July 2021 (over a period of 9 months) were analyzed in the study. All consecutive patients with persistent cough and dyspnoea lasting for more than 3 months after positive COVID test result were included. Patients below the age of 18 years were excluded from the analysis.

The variables used in the study were age more than 60 years, gender, comorbidities, presence of more than 5 symptoms as initial manifestation during the disease (fever, loss of smell, loss of taste, cough, breathlessness, hemoptysis , diarrhea, fatigue, headache), home isolation and treatment, severe illness(moderate or severe), initial CT scoring (more than or equal to 8), presence of parenchymal band or reticulations in CT scan, preexisting respiratory illness(COPD or asthma or ILD),initial high inflammatory markers (CRP, LDH, ferritin, d-dimer) and rising titre of inflammatory markers within the first 2 weeks of illness.

2.1. Statistical analysis

Categorical and quantitative variables were expressed as frequency (percentage) and mean ± SD respectively. Chi-square test was used to find association between categorical variables. Odds ratio with 95 % CI was used to explain association of long- COVID pulmonary symptoms with selected variables. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. Statistical analysis was performed by using a statistical software package SPSS version 20.0.

3. Results

Five hundred and four patients were included in the study. The mean age was 49.9 ± 16.8 SD. Majority of the patients were below 60 years of age (72.4%, N=365) compared to those above the age of 60 years (27.6%, N=139). Common comorbidities included diabetes mellitus (26.6%, N=134), hypertension (24.8%, N=125), coronary artery disease (12.7%, N=64), dyslipidemia (6.0%, N=30), hypothyroidism (5.0%, N=25), COPD (4.0%, N=20), asthma (19.8%, N=100) and others (8.9%, N=45) [Table 1].

Table 1 Percentage distribution of sample according to comorbidities

Comorbidities	Count	Percent
Nil	172	34.1
Diabetes Mellitus	134	26.6
Hypertension	125	24.8
Coronary Artery Disease	64	12.7
Dyslipidemia	30	6.0
Hypothyroidism	25	5.0
COPD	20	4.0
Asthma	100	19.8
Others	45	8.9

More than 5 symptoms (which included either fever, loss of smell, loss of taste, cough, breathlessness, hemoptysis, diarrhea, fatigue and/or headache) were present in 28.2 %(N=142) patients. D-dimer was normal in 39.3 % (N= 198). Individuals with abnormal CRP value was higher with 78.4 %(N=395). Out of 88 patients with radiological findings, 76 (86.4%) had parenchymal band on CT scan. CT score (CORADS score) less than or equal to 8 were seen in 50.3 %(N=82) [Table 2].

Table 2 Percentage distribution of sample according to selected variables

		Count	Percent
More than 5 symptoms	Present	142	28.2
	Absent	362	71.8
D-Dimer	Normal	198	39.3
	Abnormal	306	60.7
CRP	Normal	109	21.6
	Abnormal	395	78.4
Rising titre of inflammatory markers	Present	316	62.7
	Absent	188	37.3
Parenchymal band on CT scan	Present	76	86.4
	Absent	12	13.6
CT score	<=8	82	50.3
	>8	81	49.7

Patients who had long -COVID pulmonary symptoms were more (N=308, 61.1%) than those who had no long -COVID pulmonary symptoms (N=196, 38.9%) [Table3].

Table 3 Percentage distribution of the sample according to Long COVID pulmonary symptoms

Long COVID pulmonary symptoms	Count	Percent
Present	308	61.1
Absent	196	38.9

Patients who took home oxygen treatment were 64 (18.6%) and those who took hospital treatment were 146 (44.4%) [Table 4].

Table 4 Percentage distribution of sample according to treatment

Treatment		Count	Percent
Home oxygen	Yes	64	18.6
	No	280	81.4
Treatment taken	Hospital	146	44.4
	FLTC	3	0.9
	Home	180	54.7

Long -COVID pulmonary symptoms were present in 245 patients (67.1 %) of age less than or equal to 60, among which 162 (69.2%) were females. 78.2 % patients had more than 5 symptoms. 53.3 % (N= 177) patients with comorbidities were associated with long -COVID pulmonary symptoms whereas significantly higher (N= 276, 87.3 %, $p<0.01$) number

of patients were associated with rising titre of inflammatory markers. 276 patients (87.3%, p<0.01) with long- COVID pulmonary symptoms were associated with rising titre of inflammatory markers. 150 patients (83.3%, p<0.01) who took home treatment were associated with long- COVID pulmonary symptoms [Table 5].

Table 5 Association of Long COVID pulmonary symptoms with selected variables

		Long covid pulmonary symptoms				**χ^2**	**p**	**Odds (95% CI)**
		Present		**Absent**				
		Count	**Percent**	**Count**	**Percent**			
Age	<=60	245	67.1	120	32.9	20.13	p<0.01	1
	>60	63	45.3	76	54.7			2.46 (1.65 – 3.67)
Gender	Male	146	54.1	124	45.9	12.12	p<0.01	1.91 (1.33 – 2.76)
	Female	162	69.2	72	30.8			1
Co morbidities	Yes	177	53.3	155	46.7	24.89	p<0.01	2.80 (1.85 – 4.22)
	No	131	76.2	41	23.8			1
More than 5 symptoms	Present	111	78.2	31	21.8	24.21	p<0.01	1
	Absent	197	54.4	165	45.6			30.0 (1.92 – 4.70)
CRP	Normal	57	52.3	52	47.7	4.55*	0.033	1.59 (1.04 – 2.44)
	Abnormal	251	63.5	144	36.5			1
Rising titre	Present	276	87.3	40	12.7	245.26	p<0.01	1
	Absent	32	17.0	156	83.0			33.64 (20.31 - 55.72)
Parenchymal band on CT scan	Present	76	100.0	0	0.0	19.67	p<0.01	-
	Absent	9	75.0	3	25.0			-
D-dimer	Normal	124	62.6	74	37.4	0.32	0.575	-
	Abnormal	184	60.1	122	39.9			-
CT score	<=8	79	96.3	3	3.7	0	0.968	-
	>8	78	96.3	3	3.7			-
Home oxygen	Yes	50	78.1	14	21.9	9.38**	0.002	2.99 (1.45 – 6.17)
	No	256	91.4	24	8.6			1
Treatment taken	Hospital	140	95.9	6	4.1	14.21	p<0.01	1
	FLTC	2	66.7	1	33.3			11.67 (0.92 – 147.3)
	Home	150	83.3	30	16.7			4.67 (1.89 – 11.55)

**: - Significant at 0.01 level, *: - Significant at 0.05 level

Patients with more than 60 years of age, male gender, presence of comorbidities, rising titre of inflammatory markers within the first 2 weeks of illness,presence of parenchymal bands on CT scan and those with home oxygen therapy who took hospitalized treatment were associated with long- COVID pulmonary symptoms.

4. Discussion

Bai F etal suggested that female gender was independently associated with long -COVID syndrome than males [4]. Pela G etal also demonstrated that females were more symptomatic than males not only in the acute phase but also at follow-up. Gender was found to be an important determinant of long -COVID-19 syndrome because it is a significant predictor of persistent symptoms in females, such as dyspnoea, fatigue, chest pain, and palpitations [5]. In the present study, males constituted the majority 53.6 % (N=270) compared to females 46.4% (N=234). In the present study, the mean age was 49.9 ± 16.8.

In their study, Zhao M, Wang M etal suggested that the symptoms of the elderly patients (60-74 years old) were more atypical, with more comorbidities, secondary infection, organ injuries, immune dysfunction and a higher risk of critical illness. Older age was an important risk factor for mortality [6].

Sanyaolu A etal demonstrated that fever (88.8%) is the most common symptom, followed by dry cough (68%) and fatigue (33%). Other symptoms noted were productive cough (28.5%), shortness of breath (17%), muscle pain (14.4%), sore throat (11.4%), and headache (10.2%). The least common symptoms were diarrhea (4.4%), nausea and vomiting (4.1%), rhinorrhea (3.2%), abdominal pain (0.16%), and chest pain (0.11%) [7]. In the present study more than 5 symptoms which include fever, loss of smell, and loss of taste, cough, breathlessness, hemoptysis, diarrhea, fatigue and headache were present in 142 patients (28.2%).

According to Daines L etal breathlessness, cough and chest pain were the most commonly reported respiratory symptoms associated with long -COVID. In hospitalized patients, abnormalities on lung function testing or chest imaging were observed less commonly at 12 months compared to six months since discharge [8]. In the present study long-COVID pulmonary symptoms were manifested in 308 patients (61.1%) and parenchymal bands on CT scan were present in 76(86.4%) patients. Those adult patients with persistent cough and/or breathing difficulty for more than 12 weeks after positive COVID 19 tests were included in the present study.

In their study on prolonged elevation of D-dimer levels in convalescent COVID-19 patients, Townsend L etal suggested that increased D-dimer levels (>500 ng/ml) were observed in 25.3% patients up to 4 months post-SARS-CoV-2 infection. On univariate analysis, elevated convalescent D-dimers were more common in COVID-19 patients who had required hospital admission and in patients aged more than 50 [9]. In the present study, elevated D-dimer values were present in 306 (60.7%) patients with long- COVID pulmonary symptoms and elevated D-dimers were common in hospitalized patients who were of the age less than or equal to 60. Pérez-González etal suggested that persisting symptoms are common after COVID-19 especially in hospitalized patients compared to outpatients (52.3% vs. 38.2%) [10]. In the present study, persisting pulmonary symptoms were more in those who took home treatment (N=150, 83.3%) compared to hospitalized patients (N=140, 95.9%).

Lei etal suggested that the initial chest CTs showed 27 (58.7%) patients had ground-glass opacity, 19 (41.3%) had ground glass and consolidation, and 35 (76.1%) patients had crazy-paving pattern. None of the patients who died had fibrosis in contrast to six (15%) patients who recovered from COVID-19. Most patients had subpleural lesions (89.0%) as well as bilateral (87.0%) and lower (93.0%) lung lobe involvement. Diffuse lesions were present in four (67%) patients who succumbed to coronavirus but only one (2.5%) patient who recovered ($p < 0.001$). In the death group of patients, the total CT score was higher than that of the recovery group ($p = 0.005$) [11]. In the present study, parenchymal band on CT scan were present on (N=76) 86.4% patients while parenchymal bands were absent on (N=12) 13.6 % patients.

Francone M etal found out that CT score was significantly higher in critical and severe than in mild stage ($p < 0.0001$), and among late-phase than early-phase patients ($p < 0.0001$). CT score was significantly correlated with CRP ($p < 0.0001$, $r = 0.6204$) and D-dimer ($p < 0.0001$, $r = 0.6625$) levels. A CT score of ≥ 18 was associated with an increased mortality risk and was found to be predictive of death [12]. In the present study, long- COVID pulmonary symptoms were non significantly correlated with CT score ($p>0.01$) and D-dimer values ($p>0.01$). Long -COVID pulmonary symptoms were present in 96.3 % (N= 79) patients with CT score <= 8.

According to O'Mahoney LL etal, on average, at least 45% of COVID-19 survivors, regardless of hospitalization status, went on to experience at least one unresolved symptom (mean follow-up 126 days). Fatigue was frequently reported across hospitalized (28.4%; 95% CI 24.7%-32.5%), non-hospitalized (34.8%; 95% CI 17.6%-57.2%), and mixed (25.2%; 95% CI 17.7%-34.6%) cohorts [13]. In the present study more than 5 symptoms which include fever, loss of smell, and loss of taste, cough, breathlessness, hemoptysis, diarrhea, fatigue and headache were present initially in 142 patients (28.2%).

In their study on immunity and inflammatory biomarkers in COVID-19, Iwamura APD etal found out that Total lymphocyte count and levels of CD3+ and CD4+ T cells were decreased in severe and critical cases. Interleukin-six (IL-6) was high in mild and severe patients regardless of comorbidities. C-reactive protein (CRP) levels were increased regardless of disease severity or presence of comorbidities. High levels of D-dimer and lactate dehydrogenase were present in diabetic patients and patients who developed c. They concluded that the total lymphocyte count, CD3+ and CD4+ T cells are low, especially in severe and critical COVID-19 patients; ESR, CRP and IL-6 were elevated, independent of the severity of disease [14]. In the present study, CRP, LDH, ferritin, d-dimer were used as the inflammatory markers. Rising titre of inflammatory markers were present in 62.7 %

(N=316) patients whereas CRP levels were abnormal in 78.4 %(N=395) patients. Our study concluded that CRP levels and D-dimer values were abnormal in a greater number of subjects than the rising titre of inflammatory markers which were present in 316 patients.

The main limitation of this study was that it was a retrospective analysis. A prospective analysis is required for further helping understanding the factors leading to fibrosis.

Abbreviations

- COPD: Chronic Obstructive Pulmonary Disease.
- SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.
- CT score: CORADS score.
- CI: Confidence Interval.
- ILD: Interstitial lung Disease.
- CRP: C Reactive protein.
- LDH: Lactate Dehydrogenase.
- SD: Standard Deviation.
- ARDS: Acute Respiratory Distress Syndrome.
- IL-6: Interleukin 6.
- CD4 cells: Clusters of Differentiation cells.

5. Conclusion

This study is highly relevant since limited data is available in India regarding the predictors leading to the development of pulmonary manifestations in long- COVID. Different factors like age, gender, presence of comorbidities, asymptomatic initial disease presentation etc. may be involved in the progression of disease. Early identification of risk factors might help in preventing long term complications like pulmonary fibrosis in long- COVID.

Compliance with ethical standards

Disclosure of conflict of interest

No Conflict of interest to be disclosed.

Statement of ethical approval

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Institutional Ethics Committee- PRS Hospital.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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