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Predictors of symptom persistence and respiratory sequelae in respiratory symptomatics presenting to a post-COVID clinic

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ABSTRACT

Background: COVID-19 infection causes the persistence of respiratory symptoms and functional impairment, which require prolonged follow-up care. Identification of individuals at risk for respiratory sequelae helps in optimal follow-up and early identification of complications. **Aims and Objectives:** The present study aims to find the clinical profile, predictors of respiratory symptom persistence, and functional impairment in post-COVID patients. **Materials and Methods:** Prospective observational study was done on patients who attended the post-COVID clinic in the pulmonary medicine outpatient department (OPD) in a tertiary care center in central Kerala from June 2021 to August 2021 with persisting respiratory symptoms after becoming COVID-19 negative and evaluated with a proforma regarding clinical history and symptoms. Patients were followed up at one and 3 months. Clinical, functional, and radiological factors were assessed. They were reassessed at 3 months. Spirometry was done in those with persistent symptoms at 3 months. High-resolution computed tomography (CT) was performed in those with significant desaturation on 6-min walk test (6MWT). **Results:** Of 348 patients, 6 died, 4 lost follow-up, 12 patients had alternative diagnoses during the study period. About 29.4% were symptomatic at 3 months. CT severity score improved over 3 months and the proportion of patients with exercise-induced desaturation in 6MWT decreased over 3 months. All patients showed a restrictive abnormality except two. A significant association was found between the persistence of symptoms at 3 months and type 2 diabetes mellitus, severe illness during the initial phase, persistent elevation of inflammatory markers, and increased radiological involvement. Alternative diagnosis and treatment-related complication was seen in 12 patients, which included infections such as tuberculosis, nocardia and fungal infection, malignancy, CTEPH, and post-intubation tracheal stenosis. **Conclusion:** A minor group of severe COVID-19 pneumonia survivors have delayed resolution of symptoms with functional impairment. Improvement in spirometry lags behind clinical and radiological improvement.

Key words: COVID 19; Post-COVID; Respiratory sequelae

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INTRODUCTION

COVID-19 is caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can manifest itself with a wide spectrum of symptoms ranging from asymptomatic to life-threatening and fatal diseases. Although most of the patients recovered completely from COVID after days, some had persistent or the emergence of new symptoms following the recovery from COVID. Post-acute COVID-19 is defined as people who still have symptoms between 4 and 12 weeks after acute symptoms.[1] Post-COVID Syndrome is defined as "signs and symptoms

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that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by alternative diagnosis."[1]

A notable percentage of COVID-19 survivors had persistent respiratory symptoms such as dyspnea, cough, and chest discomfort.[2] This raises concern about the potential long-term lung damage due to COVID and its consequences. There is no clear understanding of the pathogenesis and treatment of these long-term complications of COVID-19. For the overall management of this entity, we need a holistic approach that is evidence based. This study focuses on gaining information about the evolution of symptoms in long COVID patients and identifying the predictors for symptom persistence.

Aims and objectives

1. To find the prevalence of persistent respiratory symptoms on 3-month follow-up of COVID-19 patients
2. To describe the predictors of respiratory symptom persistence and to find the clinical evolution of those symptoms during 3-month follow-up in COVID-19 patients.

MATERIALS AND METHODS

The current study was a prospective observational study done in patients attending the pulmonary medicine outpatient department (OPD) with persisting respiratory symptoms after becoming COVID-19-negative.

Inclusion criteria

All consecutive patients aged 18 years or above with a history of COVID-19, who has become COVID-negative and attending pulmonary medicine OPD with persisting respiratory symptoms within 1 month of negative COVID result, who consented to the study were included.

Exclusion criteria

Moribund patients were excluded from the study.

Those patients with previous documented exercise desaturation/resting hypoxia before COVID were excluded from the study.

The study tool was based on proforma and examination findings. The sample size for the study was calculated using the formulae-

Sample size: n=(z1–/2) 2Pq/d2

A study done in the UK on attributes and predictors of long COVID-19 by the COVID symptom study app, found that 558 had symptoms lasting more than 28 days. Among the symptomatic, 383 had a persistent cough (9.1%).[2]

P=9.1%, Q=90.9%, d=5%, n=127.

Study procedure

All COVID-19 patients with a history of polymerase chain reaction positive COVID-19 and who became negative, presenting with respiratory symptoms to pulmonary medicine OPD within 1 month of symptoms were evaluated with a proforma which included patient details, history of acute illness-symptoms, details of history focusing on comorbidities, treatment history-included details on intensive care unit (ICU) admission, ventilatory support, duration of oxygen support during the phase of illness, laboratory investigations done- neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), D dimer, and details of chest X-ray (CXR) during the acute phase of illness. Patients were followed up at 1 month and 3 months with repeat CXR, CRP, D-dimer and the clinical evolution of symptoms were analysed. 6 min walk test (6MWT) was done at 1 month and 3 months. Details of computed tomography (CT) thorax at 1 month and 3 months was also collected if available. Results of spirometry at 3 months after COVID infection in persistent symptomatic patients were also noted.

Statistical analysis

Data were numerically coded and entered into a Microsoft Excel spreadsheet. Analysis of data was done using SPSS software. Categorical variables were expressed as proportions, and quantitative variables were expressed as mean and standard deviations. Chi-square test was applied and was considered statistically significant whenever $P \leq 0.05$.

RESULTS

The study group included a total of 348 patients with respiratory symptoms, of which 6 patients died and 4 were lost to follow-up and 12 patients had alternative diagnoses during the study period. The remaining 326 patients who completed the follow-up were included in the data analysis. (Figure 1) Among 326 patients, 231 (70.8%) patients were males. Majority of the study group belonged to the age group of 41–60 years. The mean age was 51.38 years. Diabetes mellitus was the most common comorbidity (54.2%), followed by hypertension (24.5%).

At 3 months follow-up, 96 patients out of the 326 had persistence of respiratory symptoms. Cough (94%) was the most common persistent symptom, followed by fatigue (17.1%) and dyspnea (10.7%). At 3 months, CRP and D

dimer was found to be negative in all patients except two. 59 patients had a CXR suggestive of resolving COVID pneumonia at 3 months (Table 1). High-resolution CT was performed in 33 patients at 1 month and repeated at 3 months. The median CT severity index (CTSI) was 16.4 (SD 5.51) at 1 month and 10.2 (SD 3.83) at 3 months. At 1 month, 86 patients (24.7%) of 326 had exercise-induced desaturation on 6MWT, while at 3 months, only 27 (8.2%) out of 326 patients had desaturation on 6MWT (Figure 2). Out of 27, four patients had a resting hypoxemia and was continuing home oxygen therapy. A pulmonary function test (PFT) was done in 79 out of 96 symptomatic patients at 3 months. All patients showed a restrictive abnormality except two.

Significant association was found between the persistence of symptoms at 3 months and Type2 diabetes mellitus (P=0.001), COVID category C (P=0.001), dyspnea (P=0.001) or fever (P=0.001) during initial illness, hospital admission, ICU admission (P=0.001), more than 15 days of hospital stay (P=0.001), oxygen requirement, initial CRP more than 26 mg/dL (P<0.001), initial D dimer more than 996 (P=0.01), initial NLR more than 5.05 (P<0.001) (Table 1). Persistent elevation of CRP more than 11 mg/dL at 1 month (P<0.001) and elevated D dimer more than 978 ug/L at 1 month (P<0.001) showed significant association with persistence of symptoms in post covid patients (Table 2). The radiological predictors of symptom persistence were more than 4 zones involvement in CXR at 1 month (P=0.001) and 1 month CTSI more than 13 (P<0.001).

Alternative diagnoses such as lung malignancy, tuberculosis, ILD, nocardiosis, aspergillosis, mucormycosis, and post-intubation tracheal stenosis were seen in 12 patients. Two patients who had a pulmonary embolism during acute COVID-19 were found to have persistent pulmonary artery hypertension.

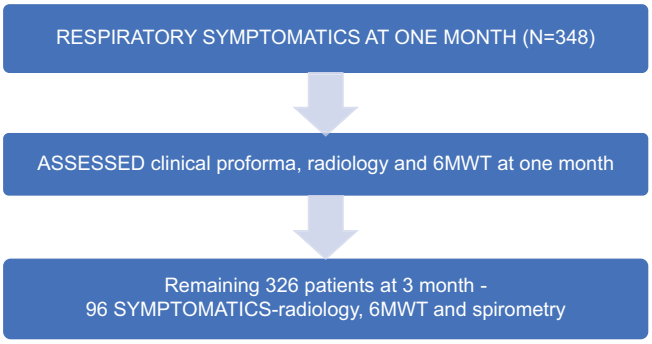

Figure 1: Follow-up of patients

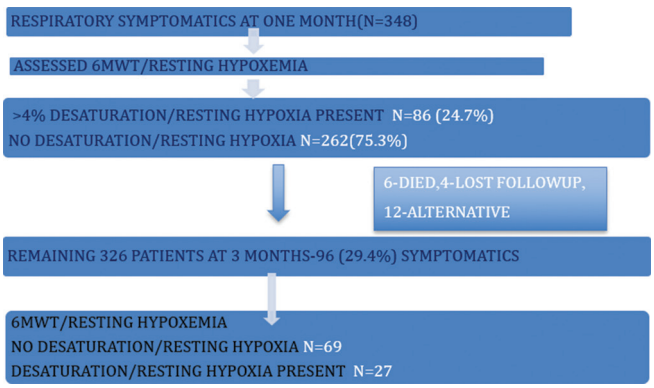

Figure 2: 6MWT in respiratory symptomatics post-covid

DISCUSSION

Among the 326 symptomatic patients at 1 month, on follow-up, 96 (29.4%) patients had persistence of symptoms at 3 months. The prevalence rates of long-lasting COVID-19 sequelae in the literature vary significantly based on the geographic location of the study population and patient background characteristics.[3] In a study from the United Kingdom, 74% of patients out of 110 individuals demonstrated post COVID sequele.[4] while in a study of 1234 individuals by Naik et al., in a tertiary care center in northern India, only 9.9% reported residual symptoms after 3 months.[5] The long-lasting symptoms of COVID are an indication of persistent organ damage. The symptoms of dyspnea and cough appear to be common in most studies.[6-8] and our findings were consistent with these earlier results. The development of the disease and the high CRP could both be explained by macrophage activation syndrome in COVID. Inflammatory markers were negative at 3 months in all patients except two, which suggests that the inflammation had subsided overtime. The human immune system's capacity to fight infections is reduced with age, which makes them more vulnerable to severe types of COVID-19. In our study, age more than 50 was found to be a predictor of symptom persistence. In our study, gender did not show a statistically significant association with persistence of symptoms. However, this is in contrast to numerous other research that found that female individuals had a higher prevalence of long COVID

Table 1: Comparison of patient demographics at 1 month and 3 months

Variables	At 1 month	At 3 months
Total symptomatic patients	326	96
Category of COVID during the initial phase	Mild-223 Moderate-32 Severe-71	Mild-0 Moderate-26 Severe-70
CRP elevated	188	2
D Dimer elevated	179	2
CXR abnormal	118	59
Mean CT score	16.4 (SD 5.51)	10.2 (SD 3.83)

SD: Standard deviation, CT: Computed tomography, CXR: Chest X-ray, CRP: C-reactive protein

Table 2: Patient characteristics

Variables	Symptomatic at 3 months	Asymptomatic at 3 months (%)	P-value
Male	70 (21.5)	161 (49.3)	0.065
Female	26 (8)	69 (21.2)	
Age			
1–20	0	1 (0.3)	0.003
21–40	7 (2.1)	51 (15.6)	
41–60	64 (19.6)	134 (41.1)	
>60	25 (19.9)	44 (13.4)	
Initial symptoms			
Dyspnea	86 (26.4)	24 (7.4)	0.001
Cough	95 (29.2)	229 (70.2)	
Chest pain	4 (1.2)	0	
Fever	70 (21.4)	17 (5.3)	0.003
Hemoptysis	3 (0.9)	0	
Fatigue	79 (24.2)	212 (65)	
Comorbidity			
Diabetes mellitus	54 (16.5)	71 (21.8)	0.001
Hypertension	34 (10.4)	46 (14.1)	
Cardiac disease	15 (4.6)	23 (7.05)	
Respiratory	5 (1.5)	1 (0.3)	
Others	18 (5.5)	7 (2.1)	
Category of COVID			
Mild	0	216 (66.3)	0.001
Moderate	26 (7.8)	12 (3.6)	
Severe	70 (21.4)	1 (0.3)	
Hospitalization during acute COVID (before becoming negative)			
0-15 days	51 (15.6)	230 (70.5)	0.001
16–30 days	41 (12.5)	0	
31–45 days	2 (0.6)	0	
46–60 days	1 (0.3)	0	
>60 days	1 (0.3)	0	
ICU admission during acute COVID			
ICU admitted	59 (18)	3 (0.92)	0.001
Not admitted	37 (11.3)	227 (69.6)	
Oxygen requirement during acute COVID			
No oxygen requirement	13 (3.9)	217 (66.5)	0.001
Low flow devices	33 (10.1)	12 (36.8)	
High flow devices	50 (15.3)	1 (0.3)	
Initial D dimer			
<996 µg/L	13 (3.9)	216 (66.2)	0.01
996 or more	83 (25.4)	14 (4.2)	
Initial NLR			
<5	20 (6.1)	178 (54.6)	<0.001
5 or more	76 (23.3)	52 (15.9)	
One month CRP			
<11mg/dL	23 (7)	227 (70)	<0.001
11 or more	73 (22)	3 (0.9)	
One month D dimer			
<978 µg/L	83 (25.4)	230 (70.5)	<0.001
978 or more	13 (3.9)	0	
One month CXR			
<4 zones	40 (12.2)	229 (70.2)	0.001
4 or more	56 (17.1)	1 (0.3)	
CTSI			
<13	21 (6.4)	228 (69.9)	<0.001
13 or more	75 (23)	2 (0.6)	

All percentage given in this table is out of the total number of patients n=326, CXR: Chest X-ray, CTSI: CT severity index, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio

than males. Type 2 diabetes has been shown to increase the risk of long COVID.[9] This might be because of persistent inflammation and insulin resistance, which cause more severe immunological reactions after acute SARS-CoV-2 infection and results in COVID sequelae.

Acute COVID-19 infection causes disturbance in the immune system response in patients, and this predisposes to a low-grade inflammation state which may continue over the subacute phase. CRP level may be a biomarker of disease severity in COVID-19 and may also be a predictor of persistent symptoms thereafter. In our study, Initial CRP more than 26 mg/dL was found to be a predictor of the persistence of symptoms at 3 months.

In our study, all patients had a radiological improvement on follow-up at 3 months compared to 1-month CXR. However, in a prospective study by Arnold et al., 13.6% of patients showed a persistent chest radiograph abnormality after 3 months.[4] According to estimates, one-third of COVID-19 survivors with severe pneumonia develop pulmonary fibrosis.[10] Ground glass opacities and consolidation resolved on the follow-up CT. Interstitial thickening, fibrous stripes, and traction bronchiectasis were the features suggestive of fibrotic changes which were found in follow-up CT at 3 months in our study according to a systematic review and meta-analysis of 15 studies which included more than 3000 patients, majority of patients (55.7%) on follow-up CT scans after COVID-19 at 1–6 months after discharge had residual CT abnormalities.[10]

A better assessment of the COVID sequelae may be provided by quantitative CT. In our study, all patients showed an improvement in CTSI at 3 months compared to 1 month and the mean CT score was 10.2 at 3 months. CTSI more than 13 at 1 month was found to be significantly associated with post-COVID sequelae (<0.001). Similar research conducted on 192 patients by Saad et al., revealed that CTSI was substantially greater in patients with post-COVID syndrome than in controls (P=0.001).[11]

In our study, at 3 months, 8.2% of patients had desaturation on 6MWT. The proportion of patients having significant desaturation (>4%) decreased from 24.7% to 8.2% at 3 months. Observations were similar to a study on 6MWT by Derbel et al., among North African long covid patients, in which 12.5% of patients had desaturation on 6MWT at 3 months after COVID infection.[12]

At 3-month follow-up most patients showed radiological and clinical improvement as evidenced by improvement in CTSI and 6MWT, but PFT showed restrictive lung abnormality (<70%) at 3 months in 80% of respiratory

symptomatic patients. In a study by Salem et al., 50% of post-COVID patients had restrictive lung impairment (P=0.026).[13]

A small portion of COVID patients develop fungal or bacterial co-infections as found in the study, but it is reportedly less than that of the previous influenza pandemic. Patients may also develop treatment-related complications. Accurate identification of alternate diagnosis is crucial in providing appropriate care and management.

The present study emphasizes that clinical, physiological, and radiological monitoring is required for all COVID-19 survivors, especially those patients with severe illness. These patients need to be followed up for detection of physiological dysfunction, for an early intervention, rehabilitation, and also timely detection of treatment-related complications.

Limitations of the study

Single-center study.

CONCLUSION

- COVID-19 disease survivors, especially those who experienced the severe acute phase, can have delayed resolution of symptoms and in a minor group, the symptoms persist with sequelae
- Persistence of symptoms in post-COVID phase was significantly associated with T2DM, initial severity of illness, duration of hospitalization, extent of radiological involvement, and high inflammatory markers during the initial phase
- Improvement in PFT is lagging behind clinical and radiological improvement
- Persistent symptoms may also be due to treatment-related complications and alternative diagnoses.

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Authors Contribution:
ASK- Literature survey, implementation of study protocol, data collection, data analysis, statistical analysis and interpretation, manuscript preparation; V**KP**- Concept, design of study, clinical protocol, data analysis and interpretation, manuscript editing; **SM**- Data analysis and interpretation, literature survey, manuscript preparation editing and revision, preparation of figures and tables; **JS-** Literature survey, data interpretation, manuscript revision.

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