Original Article

Insights in the Management of Long COVID-19: Preliminary Observations

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ABBRIVATIONS USED IN THIS ARTICLE

SARS-CoV-2 = Severe Acute Respiratory Syndrome-Coronavirus-2
LC-ILD = Long COVID-Interstitial Lung Disease
LC-OAD = Long COVID-Obstructive Airway Disease
6MWT = Six-Minute Walk Test
GGOs = Ground-Glass Opacities
RT-PCR = Reverse Transcriptase-Polymerase Chain Reaction
SpO_2 = Arterial Oxygen Saturation
HRCT = High Resolution Computed Tomography
mMRC = modified Medical Research Council
PY = Pack Years
LMWH = Low Molecular Weight Heparin
WNL = Within Normal Limits
Mpred = Methylprednisolone
Dexa = Dexamethasone
Hydrocort = Hydrocortisone

Abstract

Background. Many patients suffer from various manifestations even after four weeks of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) positivity and they are labelled as "Long COVID". Guidelines on pharmacological management of these patients are lacking till date.

Methods. The present study is a retrospective analysis of "Long COVID" patients presenting to one of the units of Viswanathan Chest Hospital of our Institute between June 2020 and December 2020. All the records of these patients were analysed. Inclusion criteria was no pre-existing pulmonary disease and availability of follow-up visits. Systemic steroids had been given to patients with (a) resting hypoxia or (b) exertional desaturation along with radiological abnormalities, categorised as long COVID-interstitial lung disease (LC-ILD). The patients with breathlessness and wheeze or rhonchi on auscultation were categorised as long COVID-obstructive airway disease (LC-OAD). Inhaled corticosteroid and bronchodilators were given to them.

Results. Out of the 3363 patients provided consultation in the OPD, 50 patients were categorised as of long-COVID. Only 10 patients fulfilled the inclusion criteria and were included in the present study. Two patients had hypoxia at rest and three patients with significant desaturation on six-minute walk test (6MWT). On chest radiography, six patients had bilateral lower zone reticulations/non-homogeneous opacities. High resolution computed tomography confirmed ground-glass opacities (GGOs) in five of them. There were seven patients of LC-ILD, 2 of LC-OAD and 1 of "long COVID cough". LC-ILD patients responded to oral steroid therapy and showed clinical, radiological as well as functional improvement. In these patients both resting hypoxia and exertional desaturation disappeared. Also improvement in 6MWT distance was observed in these patients. Long COVID-OAD patients responded well to inhaled corticosteroids and bronchodilators with symptomatic and functional improvement.

Conclusions. Patients of LC-ILD responded well to systemic steroids and LC-OAD to inhaled corticosteroids and bronchodilators. Despite the small number of patients, the present study provides a road-map for the management of "long COVID" pulmonary sequalae till large scale studies are being done.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is highly infectious and is responsible for the coronavirus disease 2019 (COVID-19) pandemic.[1] Although SARS-CoV-2 primarily affects lungs, but it may involve almost all major organs of the body.[2] Many patients suffer from a variety of symptoms even after recovering from SARS-CoV-2 infection ranging from cough, fatigue to exertional dyspnoea and serious cardiac or neurological manifestations.[3] These symptoms and signs which persist or manifest after acute COVID-19 have been labelled as "Long COVID".[4]

Although guidelines have emerged on the management of long COVID[4,5] but discrete guidance on pharmacological management of various manifestations of long COVID is still not well defined. Treatment modalities which can be used for the management of respiratory manifestations of long COVID include supplemental oxygen, oral corticosteroids, oral acebrophylline, oral antifibrotics, combination of inhaled corticosteroid and long-acting beta-2 agonist and other supportive treatments. Although these modalities have been widely used to manage similar symptoms for other respiratory diseases, their role in the management of long COVID is an area of research. Hence, a retrospective analysis of patients presenting with the long COVID and the effect of various treatment modalities on their disease course and outcome was done in the present study.

Material and Methods

Subsequent to the rise in the recovery from COVID-19 in the population, there has been a gradual increase in the number of patients presenting to us with post-acute COVID persistent signs and symptoms.

A retrospective analysis of the long COVID patients presenting to one of the units of the outpatient department of the Viswanathan Chest Hospital of our Institute between June 2020 and December 2020 was done. The criteria used for diagnosing long COVID patients was symptoms persisting beyond four weeks from the positive RT-PCR (reverse transcriptase-polymerase chain reaction) for SARS CoV-2.[4] All baseline and follow-up visit records of the long COVID patients pertaining to the history, clinical examination findings, radiology, functional assessment and treatment given were collected and analysed. Only the patients with no pre-existing pulmonary disease and with subsequent follow-up visits were included in the present analysis.

We could not find any well-defined guidelines on the pharmacological management of the long COVID. Hence, we follow the general principles of management of pulmonary diseases for such patients. Systemic steroids were given for the following indications: (a) resting hypoxia–SpO_2<90% on room air or (b) six-minute walk test (6MWT) showing significant desaturation (≥4% fall in oxygen saturation), along with findings of ground-glass opacities (GGOs) or reticulations or parenchymal bands on high resolution computed tomography (HRCT) of thorax. Also, simultaneously, any active infection/alternate pathology was ruled out by blood and sputum examinations and other investigations as required. The prescribed usual dose of steroids (prednisolone) was 0.25-0.5 mg/kg body weight of for 1-2 weeks followed by weekly tapering to half of the previous dose titrated to clinical response. The equivalent doses of deflazacort were preferred.

Institutional Ethics Committee of the Institute approved the study design and informed consent was also obtained from the participants.

Results

A total of 3363 patients were provided consultation and treatment in the OPD of the Viswanathan Chest Hospital of our Institute during the study period. Out of them 50 patients were found to be have long COVID symptoms. Out of these 50 long COVID patients, 10 patients were found to fulfil the criteria of having (a) available follow-up visits and (b) also not suffering with any pre-existing respiratory disease. These 10 patients were included in the present study. Baseline characteristics alongwith treatment and follow-up outcomes of these patients are given in table 1.

The minimum age in the study cohort was 19 years and the maximum was 69 years. There were three females. All patients were non-smokers, except two reformed smokers. Hypothyroidism was present in two patients and only diabetes mellitus in two patients. One patient had both diabetes mellitus and hypertension. Two patients had undergone home isolation whereas rest all patients had a history of hospitalisation. Out of the eight patients treated in a hospital setting, five required oxygen during COVID-19 treatment. Seven of these patients had been given systemic steroids during the treatment. Injection Remdesivir had been given to three patients and one of these patients had history of invasive mechanical ventilation. One patient had directly come to us for consultation after discharge from COVID hospital. In other patients, the duration of the presentation varied from 3 days to 102 days (>14 weeks) [Table 1].

Nine patients had cough and seven had dyspnoea. Two patients had mMRC (modified Medical Research Council) grade 4 dyspnoea and were also hypoxic at rest. On auscultation, four patients had basal fine

Table 1. Baseline characteristics, treatment given and post-treatment follow-up of the Long COVID patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (Years)	62	68	56	65	69	45	30	49	19	59
Sex	Female	Male	Male	Male	Female	Female	Male	Male	Male	Male
Previous comorbidities	Diabetes mellitus	No	No	Diabetes mellitus	No	Hypothyroidism	No	No	Hypothyroidism	Hypertension and Diabetes mellitus
Smoking history	Never smoker	Ex-smoker (8PY)	Never smoker	Ex-smoker (25 PY)	Never smoker	Never smoker	Never smoker	Never smoker	Never smoker	Never smoker
Treatment given for COVID-19 infection	Oxygen therapy	Oxygen Inj. Mpred. LMWH	Oxygen Inj. Mpred. Inj Remdesivir Inj Enoxaparin	Oxygen Inj Hydrocort	Home isolation	Inj. Dexa Inj Enoxaparin	Home isolation	Inj. Hydrocort Inj. Enoxaparin	Invasive mechanical ventilation Oxygen Inj. Dexa Inj. Remdesivir Inj. Enoxaparin	Inj. Mpred Inj. Remdesivir Inj. Enoxaparin Plasma Therapy
Duration of presentation since discharge from COVID (in days)	0	102	11	13	12	3	83	68	33	8
Long COVID symptoms	Dyspnoea	Cough Dyspnoea	Cough Dyspnoea	Cough Dyspnoea Chest pain	Cough Dyspnoea	Cough Dyspnoea Chest pain	Dyspnoea Chest tightness	Dyspnoea Chest tightness	Cough Dyspnoea Chest tightness Wheezing	Cough Chest pain
Dyspnoea (mMRC grade)	IV	IV	II	III	III	I	I	II	II	0
Examination findings	Basal fine crepts +++	Basal fine crepts +++	WNL	Basal fine crepts +++	Basal fine crepts +++	WNL	WNL	Rhonchi +++	Rhonchi +	WNL
Hypoxia at rest (%SpO_2)	Yes (86)	Yes (85)	No (96)	No (96)	No (92)	No (99)	No (98)	No (97)	No (98)	No (97)
6MWT Distance (meters)	Not able to perform	Not able to perform	300	240	270	340	360	320	320	420
Significant desaturation (>4% from baseline)	—	—	Yes	Yes	Yes	No	No	No	No	No

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	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Chest radiograph findings	Bilateral lower zone reticulations +++	Bilateral mid and lower zone reticulations +++	Bilateral lower zone non-homogeneous opacity	Bilateral lower zone reticulations +++	Bilateral lower zone reticulations +	Bilateral lower zone non-homogeneous opacity	WNL	WNL	WNL	WNL
HRCT findings	Bilateral diffuse peripheral GGOs +++	Not performed	Bilateral diffuse sub-pleural GGOs +++	Bilateral diffuse sub-pleural GGOs +++	Bilateral diffuse GGOs and reticulations+++	Bilateral lower lobe GGOs and patches of consolidation +++	Sub-pleural GGOs +	Not performed	Not performed	Not performed
Presumptive diagnosis	Long COVID-ILD	Long COVID-ILD	Long COVID-ILD	Long COVID-ILD	Long COVID-ILD	Long COVID-ILD	Long COVID-ILD	Long COVID-OAD	Long COVID-OAD	Long COVID-Cough
Treatment given	Supplemental oxygen + oral Deflazacort 30mg x1 week 24mg x 1 week 12mg x 1 week 6mg x 1 week + oral Acebrophylline 200mg/day	Supplemental oxygen + oral Deflazacort 30mg x 2 weeks 24mg x 2 weeks 18mg x 2 weeks + oral Acebrophylline 200mg/day	Oral Deflazacort 24mg x 2 weeks 18mg x 2 weeks + oral acebrophylline-200mg/day	Oral Deflazacort 30 mg x 4 weeks 24 mg x 2 weeks 18mg x 4 weeks + oral Acebrophylline-200 mg + Inhaled Budesonide 800 mcg/day + Inhaled Formoterol 24 mcg/day	Oral Deflazacort 30 mg x 2 weeks 24 mg x 2 weeks 18mg x 2 weeks 12mg x 4 weeks 6mg x 2 weeks 6 mg alternate day x 1 month + oral Acebrophylline 200mg/day	Oral Acebrophylline 200mg/day	Oral Acebrophylline 200mg/day	Inhaled Budesonide 800mcg/day + Inhaled Formoterol 24 mcg/day + 7 days course of oral Corticosteroids Deflazacort 30 mg	Inhaled Budesonide 800 mcg/day + Inhaled Formoterol 24 mcg/day	Oral Acebrophylline 200mg/day
Follow-up duration after treatment for Long COVID (Days)	42	49	30	67	120	36	45	20	7	30
Post-treatment symptoms	No symptoms	Dyspnoea	Dyspnoea	Dyspnoea	Dyspnoea	No symptoms	No symptoms	No symptoms	No symptoms	No symptoms
Dyspnoea (mMRC Grade)	0	I	I	II	I	0	0	0	0	0
Post-treatment examination findings	WNL	Basal fine crepts +	WNL	Basal fine crepts +	Basal fine crepts +	WNL	WNL	WNL	WNL	WNL

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	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Hypoxia at rest (%SpO_2)	No (98)	No (98)	No (96)	No (96)	No (97)	No (99)	No (98)	No (97)	No (98)	No (97)
Post-treatment 6MWT distance (meters)	380	360	380	300	320	540	400	380	360	420
Gain in 6MWT distance Post-treatment (meters)	380	360	80	60	50	200	40	60	40	NIL
Post-treatment significant desaturation (>4% from baseline)	No	No	No	No	No	No	No	No	No	No
Post-treatment chest radiographic findings	WNL	Bilateral mid and lower zone reticulations +	WNL	WNL	Bilateral lower zone reticulations +	WNL	WNL	WNL	WNL	WNL
Post-treatment HRCT findings	Basal GGOs +	Bilateral sub-pleural GGOs and Fibrosis +	Not performed	Bilateral diffuse sub-pleural GGOs +	Bilateral diffuse GGOs and Reticulation +	Bilateral basal GGOs +	Not performed	Not performed	Not performed	Not performed

crepitations and two patients had rhonchi. The two patients with hypoxia at rest were not able to perform 6MWT and there were three patients with significant desaturation on 6MWT. On chest radiography, six patients had bilateral lower zone reticulations/non-homogeneous opacities while four patients had a normal radiograph. HRCT scan revealed GGOs in five of them, while in one patient bilateral lower zone reticulations. One patient with normal radiograph showed sub-pleural lower lobe GGOs on HRCT. These patients with abnormal findings on HRCT thorax were categorised as long COVID-interstitial lung disease (LC-ILD). Patients who had breathlessness with wheeze or rhonchi on auscultation, a combination of inhaled corticosteroids (budesonide 400-800 µg/day) with inhaled long-acting bronchodilators (formoterol 12-24 µg/day) was given and these patients were categorised as long COVID-obstructive airway disease (LC-OAD).

The patients with LC-ILD and fulfilling the desaturation criteria as above, were given oral steroid (deflazacort) (Table 1). There were seven patients (patients 1 to 7) categorised as LC-ILD in the present study. Two of these LC-ILD had diabetes mellitus and one had hypothyroidism. As per our selection criteria, none of these patients had any pre-existing respiratory disease. Out of these LC-ILD patients, two had resting hypoxia and three had exertional desaturation on 6-MWT. These patients were prescribed systemic steroids and clinical, radiological [Figures 1, 2, 3] and functional (6-MWT) improvement was observed (Table 1). Further, two LC-ILD patients did meet either of these two criteria for systemic steroids and were prescribed oral acebrophylline only and followed up. They also showed clinical and radiological improvement (Figures 4, 5) alongwith gain in 6-MWT distance (Table 1).

Two patients were diagnosed as LC-OAD and prescribed a combination of inhaled corticosteroids with inhaled bronchodilator. Resolution of symptoms

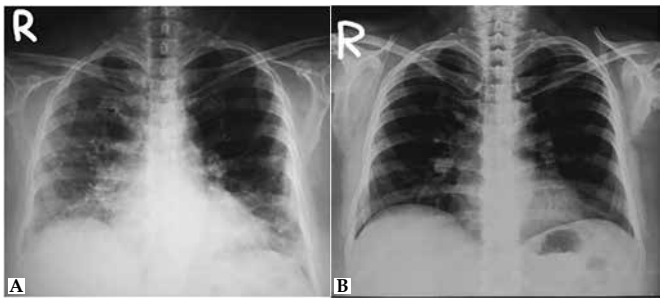

Figure 1. Patient 1 (Long COVID-ILD). Chest radiograph (postero-anterior view) showing (A) bilateral lower zone reticulations with ill-defined diaphragmatic and cardiac borders; and (B) resolution of the lower zone reticulations and clearing of diaphragmatic and cardiac borders after the treatment.

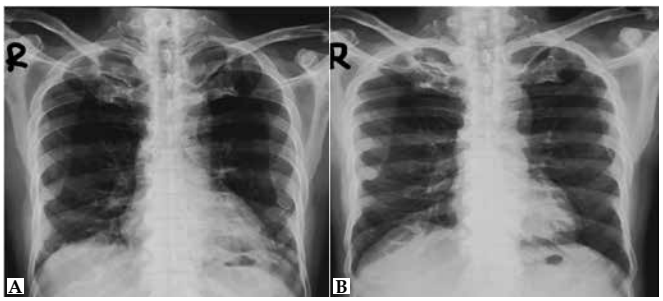

Figure 2. Patient 4 (Long COVID-ILD). Chest radiograph (postero-anterior view) on presentation (A) showing bilateral lower zone reticulations; and (B) clearing of the lower zone reticulations post-treatment.

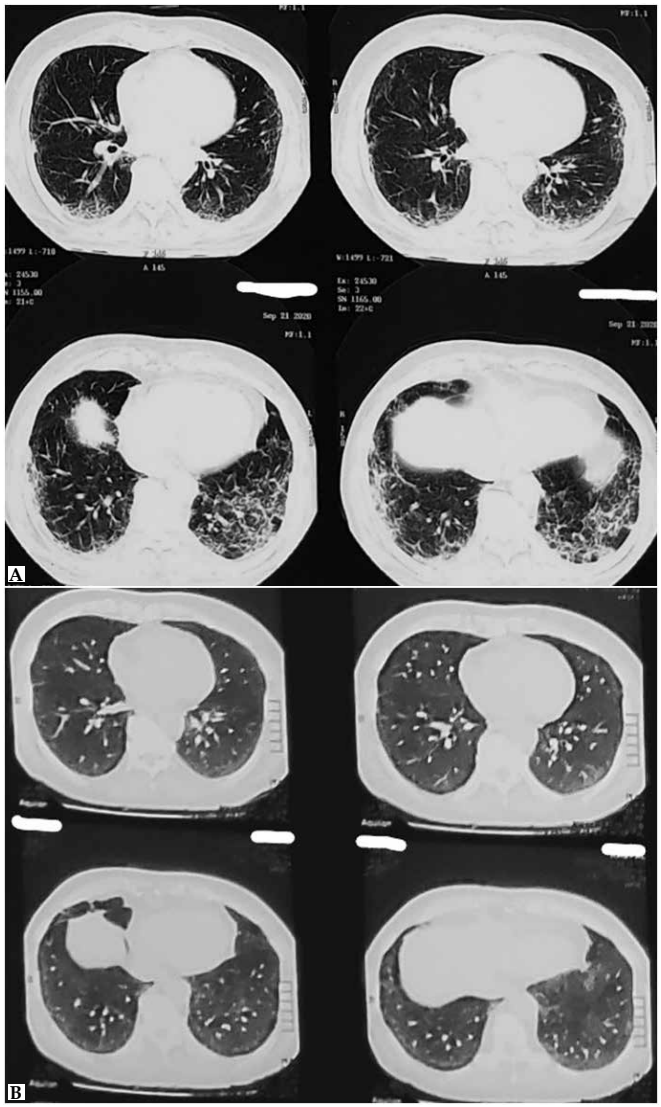

Figure 3. Patient 4 (Long COVID-ILD). Computed tomography of chest (A) suggestive of bilateral lower lobes ground-glass opacities; and (B) post-treatment CT showing decrease in the ground-glass opacities.

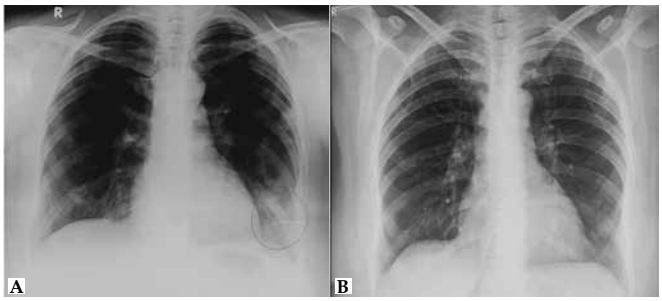

Figure 4. Patient 6 (Long COVID-ILD). Chest radiograph postero-anterior view (A) suggestive of bilateral lower zone consolidation; and (B) post-treatment chest radiograph showing resolution of the consolidation.

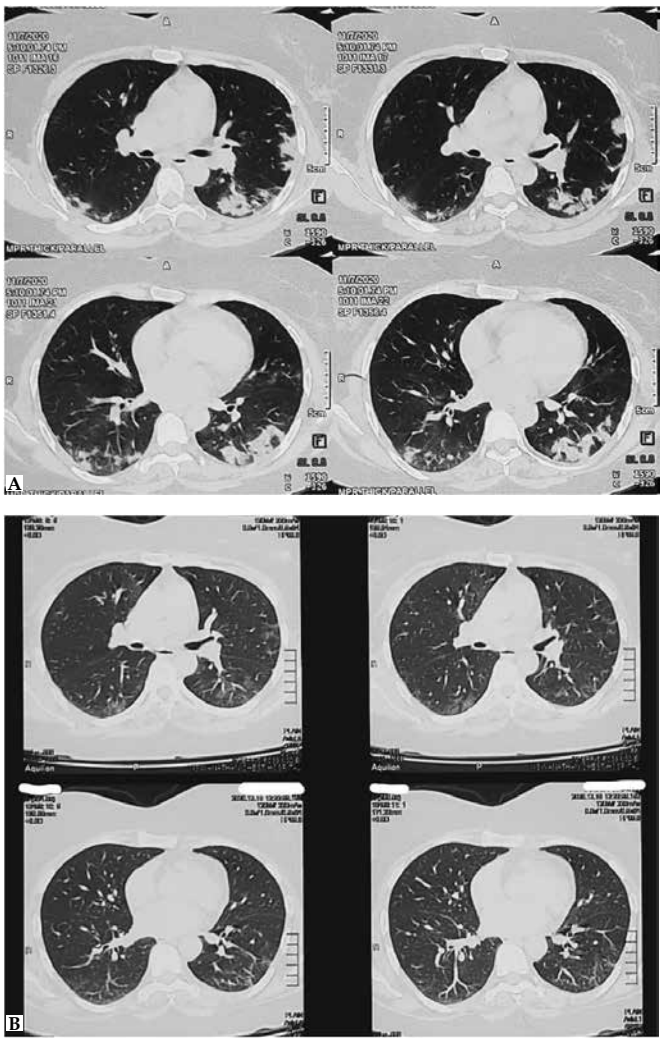

Figure 5. Patient 6 (Long COVID-ILD). Computed tomography of chest (A) suggestive of bilateral lower lobe patches of consolidation and ground-glass opacities; and (B) post-treatment CT showing resolution of the consolidation patches and decrease in ground-glass opacities.

on follow up was noted in both the patients (Table 1). One patient had dry cough and chest pain with no abnormality on examination or investigations (radiograph and ECG). The patient was treated with oral acebrophylline and showed symptomatic improvement.

The major learning points from the present study are summarised in table 2.

Discussion

COVID-19 pandemic has caused widespread mortality worldwide with 77,530,799 confirmed cases resulting in 1,724,904 deaths.[6] Patients recovered from COVID-19 still report a variety of symptoms and these patients have been categorised as "Long COVID" cases.[4] Previously, post-acute COVID-19 term has also been used in the literature for the purpose of defining symptoms that persist even after three weeks of the onset of the first symptom.[7] Even patients who had mild COVID-19 infection can experience persistent and new symptoms similar to the patients with severe COVID-19 disease.[7,8] Long COVID symptoms include fatigue, cough, dyspnoea and can range to more critical manifestations, like pulmonary fibrosis, myocarditis, renal failure and others.[2, 4]

Two patients had resting hypoxia on presentation and bilateral radiological abnormalities. They were categorised as long COVID-interstitial lung disease (LC-ILD). They were given supportive oxygen therapy along with tapering doses of steroids. *To the best of our knowledge,* there have been no definitive guidelines as yet on the pharmacological management of these long COVID interstitial/parenchymal lung disease. Although some reports have emerged of spontaneous resolution of these post-COVID radiological sequelae,[9] these patients with resting hypoxia and severe grade of dyspnoea require pharmacological management apart from the oxygen therapy. To this end we found oral steroids to have beneficial effect in the present study.

In the paucity of discrete guidance, we followed the standard treatment principles as followed in patients with interstitial lung diseases, like acute hypersensitivity pneumonitis and sarcoidosis, where steroids are the mainstay of the treatment. Also, steroids are the cornerstone of therapy for ILDs presenting with acute respiratory failure, except in cases of vasculitis associated ILDs.[10] These patients had primarily GGOs on HRCT thorax which is usually a steroid responsive radiological finding when active infections are ruled out. Both these patients responded well to steroids and started maintaining resting oxygen saturation. Their 6MWT distance also improved and did not even had exertional desaturation after steroids course. Radiology also showed improvement and steroids were tapered and stopped.

Table 2. Learning points from the present study

	Patient 1 and 2	Patient 3, 4 and 5	Patient 8 and 9
Diagnosis	Long COVID-ILD	Long COVID-ILD	Long COVID-OAD
Presentation	Dyspnoea (mMRC grade IV) Hypoxia at rest Not able to perform 6MWT	Dyspnoea (mMRC grade II, III, III) Exertional desaturation	Dyspnoea and chest tightness Rhonchi on auscultation No exertional desaturation
Radiology	Bilateral involvement on chest radiograph GGOs on HRCT in one patient	Bilateral GGOs on HRCT in all patients	WNL
Treatment Given	Oral steroids	Oral steroids	Inhaled corticosteroids and inhaled bronchodilators
Response	Resting saturation normal Dyspnoea decreased (mMRC grade 0 and I) Gain in 6MWT (380m and 360m)	No exertional desaturation, mMRC grade of dyspnoea improved (I, II, I) Gain in 6MWT (80m, 60m and 50m)	No dyspnoea No wheezing Auscultation – No rhonchi Gain in 6MWT (60m and 40m)
Learning Point	Oral steroids lead to recovery in hypoxic long COVID-ILD	Oral steroids lead to recovery in long COVID-ILD with exertional desaturation	Inhaled corticosteroids and inhaled bronchodilators provide symptomatic relief and improvement in long COVID-OAD

In the present study, three patients were maintaining resting oxygen saturation on presentation. But had dyspnoea and exertional desaturation. They were also given tapering doses of oral steroids. Post-treatment their exertional desaturation disappeared and had symptomatic relief with improvement in 6MWT distance.

Despite lack of any formal guidance on the treatment of such long COVID patients, there have been some emerging guidance which support the use of steroid therapy in such cases on an individualised basis.[5] Further we need to be cautious of immunosuppressive effects of systemic steroids, and hence, the patients should be monitored for infections. Also, the systemic steroids need to be given for short duration depending on the clinical response and should be stopped as soon as possible.

Another two patients diagnosed as LC-ILD had normal resting oxygen saturation and did not have any exertional desaturation. Hence, they were not given oral steroids. They were administered acebrophylline only. Acebrophylline is a methylxanthine and has bronchodilator and anti-inflammatory properties. It has been reported to increase the exercise tolerance and recovery from acute exacerbation of many respiratory diseases.[11] In a study by Tapadar *et al*,[12] acebrophylline was observed to cause a reduction in breathlessness and sputum production in patients with chronic obstructive pulmonary disease. Acebrophylline has also been found to improve hyper-responsive inflammatory conditions and have anti-bronchospastic activity.[13] Probably because of these mechanisms, acebrophylline treatment resulted in symptomatic relief of dyspnoea and increase in 6MWT distance in the present study patients. Although we could not confirm the lung function in these patients, because of the unprecedented COVID-19 pandemic situation which precluded the performance of pulmonary function tests at that time.

Two patients of LC-OAD had obstructive airway disease in the form of history of wheezing or rhonchi on auscultation. There was no exertional desaturation. A combination therapy of inhaled corticosteroid and inhaled bronchodilator, was given. Inhaled steroids have been advocated for use in intractable post viral cough for symptomatic relief.[14] Both the patients reported symptomatic relief after therapy and their mMRC dyspnoea scores also improved. Improvement in walk distance on 6MWT was also found in these patients.

One patient had only cough and did not have exertional desaturation. Also, both clinical and radiological examinations were within normal limits. Hence, the patient was given only acebrophylline and he reported symptomatic relief.

There is a lack of evidence-based discrete guidance at present for the management of long COVID symptoms and manifestations. The numbers of such patients with post-COVID-19 symptoms/sequelae are increasing in health-care settings and one need to manage these patients. Especially, the patients presenting with respiratory failure, severe grades of dyspnoea or exertional desaturation need utmost care, where we cannot wait for self-recovery.

There were certain limitations of the present study. First, this study being a retrospective analysis had inherent limitation of a planned approach and follow-up of the patients. Secondly, we could analyse a small pool of 'followed-up long COVID' patients but these were sans any pre-existing pulmonary diseases. Thus,

these were purely COVID affected lungs, but the subject requires further large-scale studies. Thirdly, because of the prevailing unusual COVID pandemic situation, pulmonary function tests were not being performed at that time. Hence, we could not perform the lung function assessment in these patients, although we did 6MWT for the same.

Despite our analysis being small in numbers and also lacking from a planned approach, it provides some insight into the line of management and response to therapy in long COVID respiratory manifestations. Large scale planned cohort studies are needed which would help in the development of discrete guidelines for management of long COVID manifestations.

Conclusions

Important observations from this preliminary study for the management of long COVID patients are given below.

1. Patients with long COVID-interstitial lung disease respond well to a monitored course of tapering doses of oral steroids, with doses being titrated to clinical response. Use of steroids in such cases showed clinical, radiological as well as functional improvement.
2. Patients with long COVID-obstructive airways disease respond well to inhaled corticosteroid and inhaled bronchodilators with resultant symptomatic and functional improvement.
3. Present study although comprises of small numbers of patients, provides a road-map for the management of post-COVID pulmonary sequalae, pending large scale studies.

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