Use of Cyclophosphamide in Patients with Steroid Resistant Post COVIDInterstitial Lung Disease

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Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV 2. To date; COVID-19 continues to remain at pandemic proportions. Long COVID-associated complications have been reported worldwide, among which, COVID- 19 associated interstitial lung disease (ILD) is a well-recognized long-term consequence. COVID 19- associated ILD causes significant morbidity in survivors of COVID 19 pneumonia. Although there is no evidence-based definitive treatment, immunosuppression therapy may improve the outcome of post-COVID ILD.

Methodology

Medical records of 10 patients with confirmed post COVID ILD who received IV cyclophosphamide pulse therapy were prospectively evaluated. Information regarding demographic, clinical, biochemical and radiographic characteristics were extracted.

Intravenous cyclophosphamide therapy was commenced in patients who did not show adequate clinical, radiological, and functional response to corticosteroid therapy. Sequential HRCT scans were performed on all patients for consensus. Spirometry, 6MWT and laboratory investigation trends were evaluated before and after initiating IV cyclophosphamide therapy.

Results

All post COVID ILD patients who underwent IV cyclophosphamide therapy demonstrated significant improvement in clinical, functional, radiological and laboratory parameters.

HRCT findings showed a marked response with resolution of interstitial abnormalities. HRCT with predominant ground-glass pattern showed the greatest response with near total resolution after treatment in three patients. Substantial resolution of linear fibrosis, mosaic appearance, and midzonal crazy paving patterns were also noted. Post cyclophosphamide spirometry revealed improvement in lung volumes in all patients except one. At the time of diagnosis of ILD, eight patients showed 3-6% desaturation and one patient showed 7% desaturation on 6MWT. At the end of six months of follow-up, all patients showed improvement in their functional capacity with only 1-2% of desaturation on 6MWT.

Conclusion

IV cyclophosphamide therapy was well tolerated and associated with significant improvement in post-COVID ILD resistant to steroid therapy. Therefore, it can be used effectively in the treatment of severe progressive COVID-19-related ILD. However, thesefindings cannot be generalized due to small sample size.

Keywords: *COVID-19, interstitial lung disease, IV cyclophosphamide, Sri Lanka*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS –CoV- 2) or Novel Coronavirus is the causative organism responsible for the COVID-19 pandemic which was first identified in Wuhan, China, in 2019 [1]. As of August 2022, COVID-19 has caused over 579 million infections and over 6.4 million deaths around the world [2]. By August 1st, 2022, more than
0.6 million confirmed cases and 16574 deaths were announced by the Ministry of Health, SriLanka [3].
There has been increasing evidence worldwide for long COVID-19-related post-acute and chronic persistent sequelae of multi-organ involvement [4]. The common symptoms encountered in long COVID-19 are fatigue, dyspnoea, cough, anosmia, brain fog and dysgeusia [5]. Moreover, organic system injuries involving pulmonary, cardiovascular, cutaneous, and neuropsychiatric systems have also been reported [4, 5].

Secondary interstitial lung disease (ILD) is a well-known, recognized COVID-associated complication adding further burden to pulmonary health globally [6]. In severe COVID pneumonia, steroid treatment is a standard and well-agreed protocol [7]. Inadequacy or resistance to steroids could be thought of as one reason for development of post-COVID ILD in some patients following severe COVID pneumonia.[8]. Although there are no evidence- based definitive treatment strategies, immune suppression therapy would be beneficial in ILD secondary to COVID-19 [9,10]. Therefore, steroids are used as the mainstay of treatment for COVID associated ILD in current practice. As a rapid-acting and well-tolerated drug, Intravenous (IV) cyclophosphamide is another drug effective in short-term disease conditions including systemic sclerosis, steroid-resistant NSIP (Nonspecific interstitial pneumonia), autoimmune-related ILD and organizing pneumonia [10,11]. As there is a scarcity of publications locally and internationally, our endeavour was to investigate the effectiveness of cyclophosphamide in COVID-19-related ILD, these findings will be helpful to fill the vacuum of evidence for the management of COVID associated ILD; particularly in selected cases of steroid resistant COVID-19 associated ILD.

Methodology

A retrospective observational study was carried out in the Respiratory Disease Treatment Unit two at National Hospital Kandy, Sri Lanka between 6th January 2021 to12th January 2022. Interviewer administered questionnaire was used to collect information including demographic data, symptoms, comorbidities, COVID history and complications, treatmenthistory, and investigations.

Inclusion Criteria:

(1) Patients ≥ 18 years of age.
(2) Confirmed COVID associated ILD.

Exclusion Criteria:

(1) Patients who are < 18 years of age.
(2) Patients with pre-existing ILD.
(3) Patients with underlying connective tissue disorders and Haematological disorders which can cause ILD.
(4) Patients with chronic exposure to environmental and occupational agents and medications which are known to cause ILD.
(5) Patients with incomplete medical records.
(6) Patients who did not give consent for the study.

Study patients were administered a daily dose of 1g IV methylprednisolone for three consecutive days followed by a daily dose of oral prednisolone of 0.5mg/kg at the time of diagnosis of post COVID ILD. The dose was adjusted to ideal body weight for overweight patients. Out of the studying patients, who did not show improvement in chest imaging, functional exercise capacity (6MWT), general clinical symptoms and biochemical parameters after one month of standard steroid treatment were selected and were given IV cyclophosphamide pulse therapy. The frequency and length of the therapy were decided by the consultant

respiratory physician after assessment of the patients. All patients who were undergoing cyclophosphamide therapy were monitored thoroughly for contraindications and organ functions with appropriate investigations. Informed consent was taken. IV cyclophosphamide infusion of 500mg was institute with 0.9% normal saline according to standard guidelines. Before administration of each dose of cyclophosphamide, full blood count, renal function tests, liver function tests, urinalysis, and C-reactive protein were assessed. Subsequent doses of IV cyclophosphamide were given after repeat assessment of contraindications and side effects.

Each patient was assessed regularly at two weeks intervals by the investigation team. Overall assessment of the patients was carried out during each visit. Clinical assessment was performed by symptom analysis related to ILD and other organ functions. Functional assessment of respiration was performed using six-minute walk test (6MWT) and spirometry. Initial and follow-up high-resolution computed tomography (HRCT) was done to assess radiological clearance Routine blood tests were done for biochemical assessment. Descriptive statistics were used to present the baseline data. Spirometry values were presented as percentages of the predicted values.

Results

A total of 387 COVID-19 confirmed patients were admitted, out of which, 53 (13.6%) post- COVID ILD patients were diagnosed. Out of them, the study group was composed of 10 subjects. The male and female gender was equally distributed in a 1:1 ratio. The mean age was 64.9, with an age range of 51-85 years. All male patients had a positive smoking history out of which three (60%) patients were current smokers and two (40%) were ex-smokers. The majority, eight (80%), of patients had a history of at least one comorbidity. Diabetes Mellitus was the commonest comorbidity which was present in six (60%), followed by Hypertensionin five (50%), and dyslipidaemia in four (40%).

Cyclophosphamide therapy was only commenced in the absence of clinical, functional, radiological, and biochemical improvement for corticosteroid therapy. Eight patients received IV cyclophosphamide at monthly intervals. Two patients had a 15 days interval between 1st and 2nd dose of the treatment and a monthly interval for the rest of the cyclophosphamide pulses. The number of cyclophosphamide cycles varied from four cycles for six patients, and five cycles for four patients. Multiple symptoms were observed in the post-COVID ILD patients at the time of diagnosis. **Table 1** summarizes the commonly observed symptoms at presentation and improvement at the 6 months of follow-up.

Table 1- Changes in clinical symptoms

Patient No / *Symptoms*		*P1*	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*	*P8*	*P9*	*P10*
Shortnessof Breath	**Initial**	+	+	+	+	+	+	+	+	+	+
	6 months	-	-	-	+	-	-	-	+	-	-
Cough	**Initial**	+	+	+	+	+	+	+	+	+	+
	6 months	+	-	+	+	+	-	-	-	-	-
Wheezing	**Initial**	+	+	+	-	+	+	+	-	+	-
	6 months	-	-	-	-	-	-	+	-	-	-
Arthralgia /Myalgia	**Initial**	+	+	+	+	+	+	+	+	+	-
	6 months	+	-	+	+	+	+	-	-	-	-

(+) = Symptom present, (-) = Symptom absent

Pre-intervention spirometry revealed abnormal FVC and FEV1 values in all the patients. FVC and FEV1 were improved in post-intervention except for one patient (**Figure A, B) (Table 2)**. In nine patients FVC improved significantly during the six months but declined by4% in one patient.

Figure A-Changes in the FVC during the follow up period

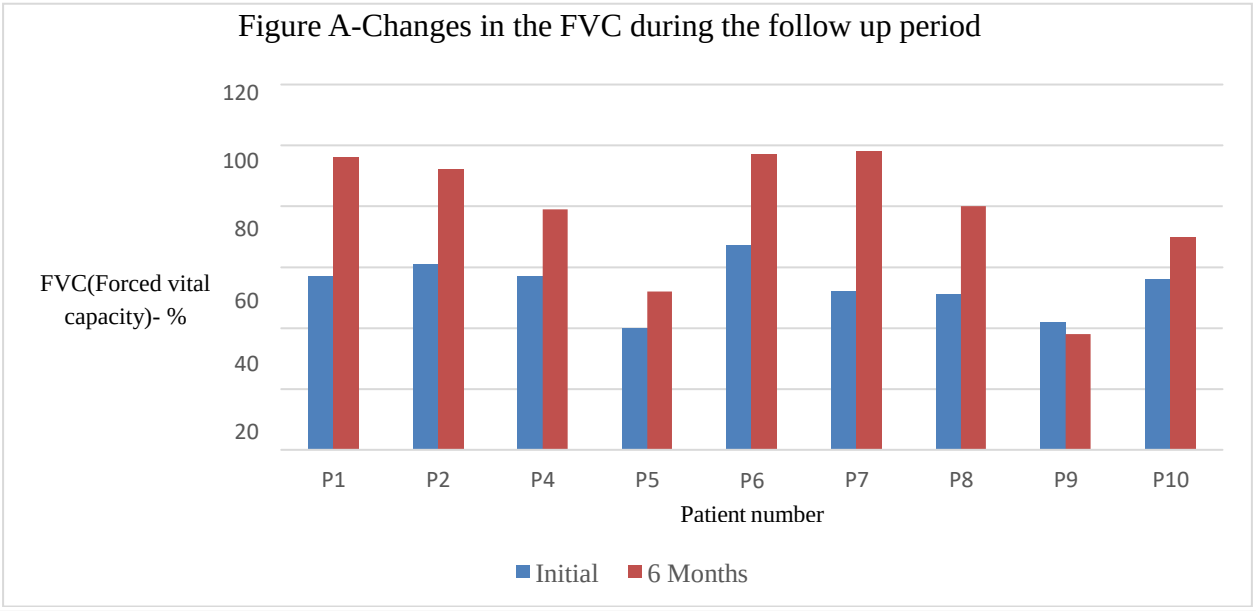


Figure B-Changes in FEV1 during the follow up period

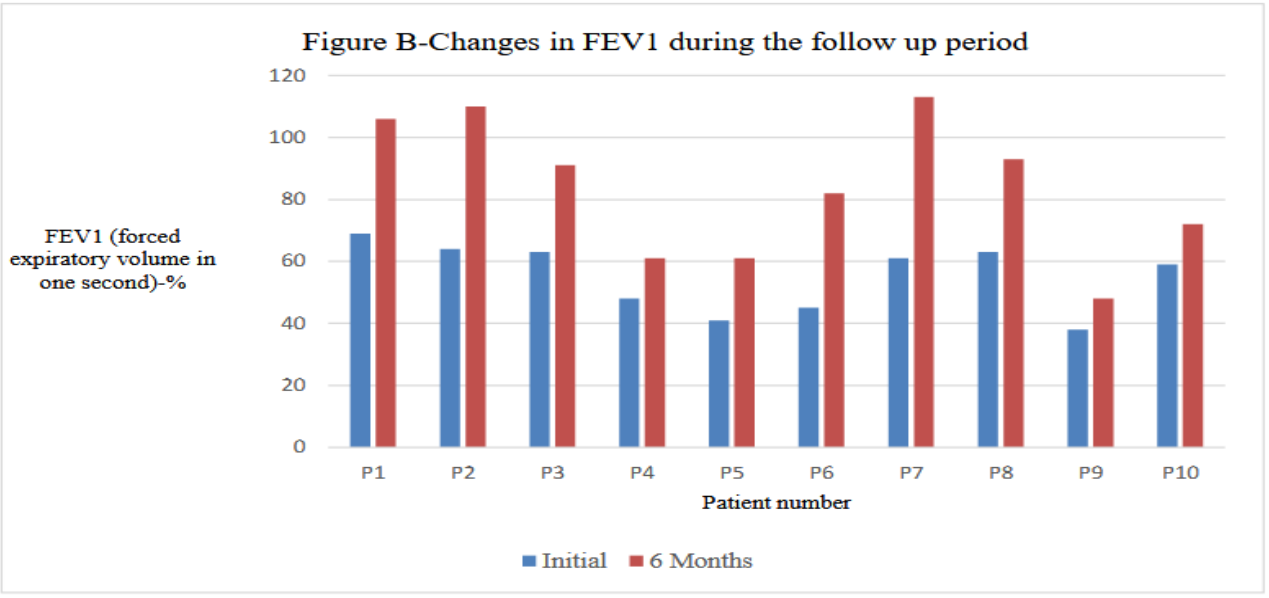


Table 2-Detailed values of the spirometry results.

Patient no.	Spirometry Values					
	FVC (%Predicted)		FEV1 (%Predicted)		FEV1/FVC (%)	
	Initial	6 months	Initial	6 months	Initial	6 months
1	57	96	69	106	121	105
2	61	92	64	110	105	115
3	57	79	63	91	113	93
4	40	52	48	61	79	97.9
5	56	66	41	61	73	96.2
6	67	97	45	82	52.1	71.7
7	52	98	61	113	97.8	110
8	51	80	63	93	123	82.9
9	42	38	38	48	69.9	96.8
10	56	70	59	72	89	81.5

FVC = forced vital capacity; FEV1 = forced expiratory volume in one second.

Initial HRCT findings

Interstitial abnormalities were bilateral in all patients. They were distributed symmetrically in eight patients while two patients had asymmetrical distribution. Multizonal involvement was found in the geographical distribution of the HRCT images. These abnormalities were seen predominantly in the middle lung zone in six patients, lower lung zones in three, and the upper lung zone in one patient. All patients had interstitial abnormalities in both the central and peripheral lungs and Nonspecific interstitial pneumonia (NSIP) was the predominant pattern of ILD **(Figure C, E, G, I)**.

On initial HRCT images, ground-glass opacity and fibrosis were present in all ten patients. Ground glass opacity was the predominant interstitial abnormality seen in six out of ten patients. Linear fibrosis, mosaic appearance, and midzonal crazy paving pattern were observed in the HRCT findings of four, two, and one patient respectively. Areas of consolidation were present in five patients, which were distributed in both the central and peripheral lungs. Bronchiectasis was observed in five patients with post-COVID interstitial lung disease.

Follow-up HRCT findings

HRCT scans after six months of treatment revealed significant improvement compared to initial scans **(Figure D, F, H, J)** HRCT of three patients with predominant ground-glass opacities on initial HRCT showed complete resolution after treatment. Other interstitial abnormalities such as linear fibrosis, mosaic appearance, and midzonal crazy paving seen on initial HRCT, also demonstrated near complete resolution following treatment with minimal residual ground glass changes, bronchiectasis, and fibrosis. In two patients, areas of consolidation were cleared with residual minimal bronchiectasis after six months of follow- up. In only one patient in the study population, bronchiectasis changes persisted for more than a year.

58-year patient (P8) with NSIP pattern.

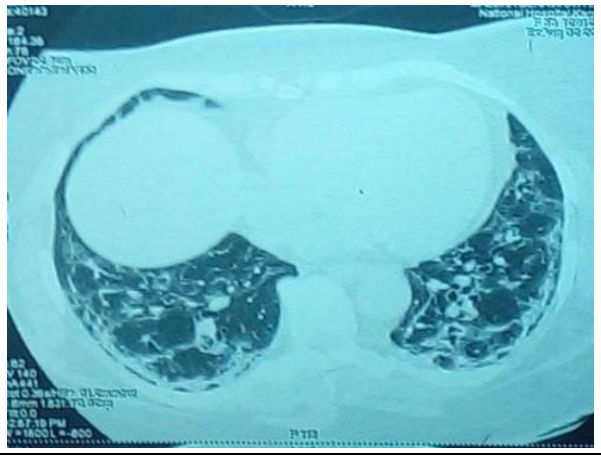


Figure (C) - Initial HRCT images showing bilateral symmetrical multizonal involvement with peripheral linear fibrosis and ground glassopacity.

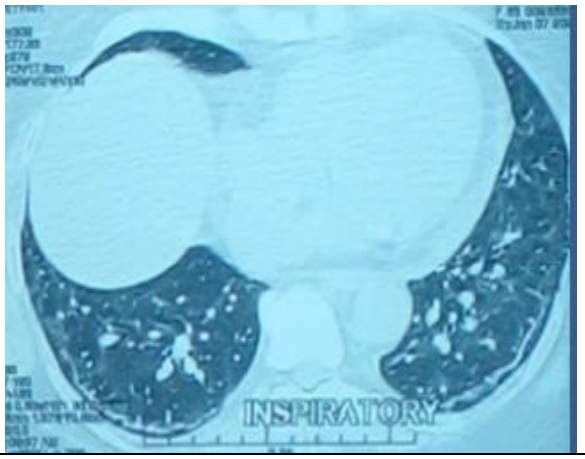


Figure (D) - HRCT scan obtained at six months follow-up showing peripheral linearfibrosis with minimal ground glass opacity.

74-year patient (P1) with NSIP pattern

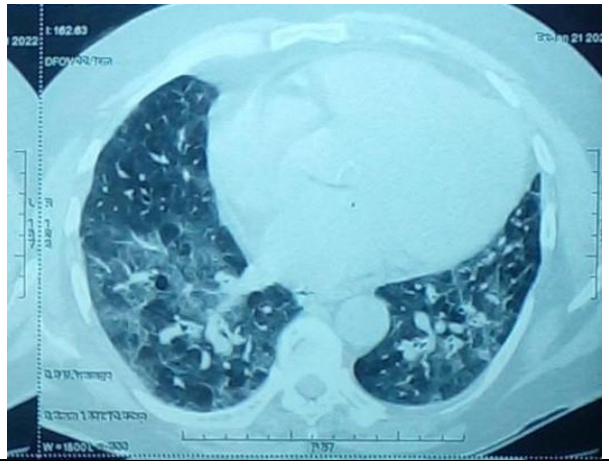


Figure (E)-Initial HRCT showing bilateral involvement, predominantly affecting the middleand lower zones, ground glass abnormalities andfibrosis, Asymmetrical mosaic pattern, and bilateral scattered bronchiectasis changes.

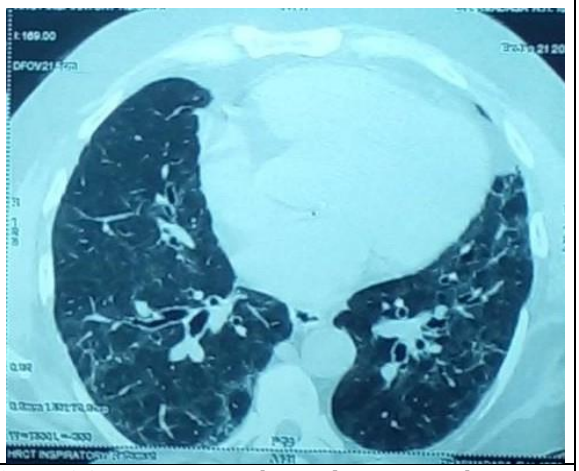


Figure (F)- HRCT scan obtained at six months follow up showing persistent residualmild ground glass opacity, bronchiectasis changes and minimal fibrosis.

35-year patient (P6) with NSIP pattern.

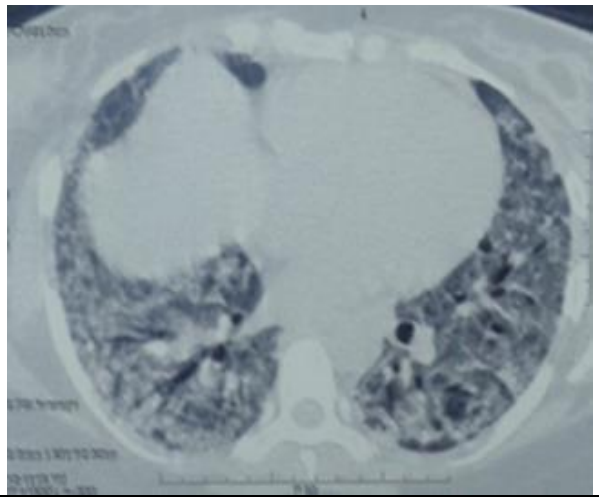


Figure (G)-Initial HRCT showing bilateral diffuse multizonal thick ground glass opacity withbronchiectasis changes.

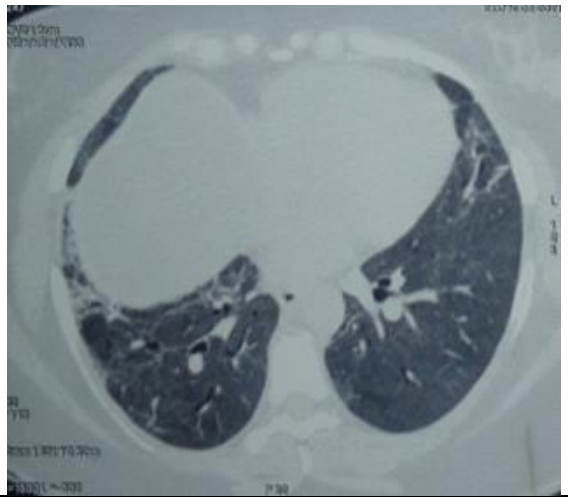


Figure (H) - HRCT scan obtained at six months follow up showing near completeresolution with minimal residual fibrosis.

79-year patient (P10) with NSIP pattern.

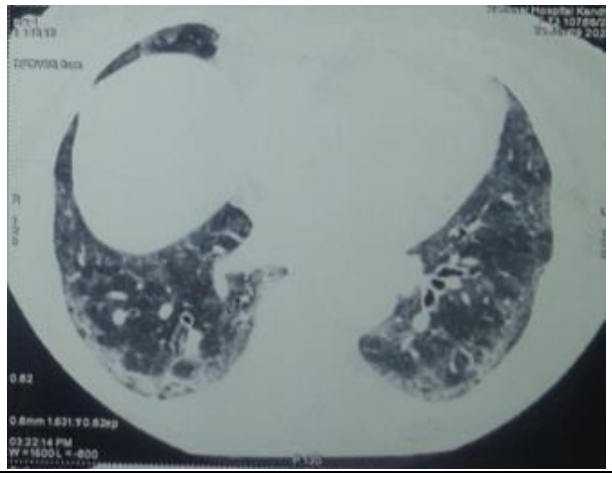


Figure (I)-Initial HRCT showing bilateral multizonal involvement with significant groundglass opacity with peripheral fibrosis and bronchiectasis changes.

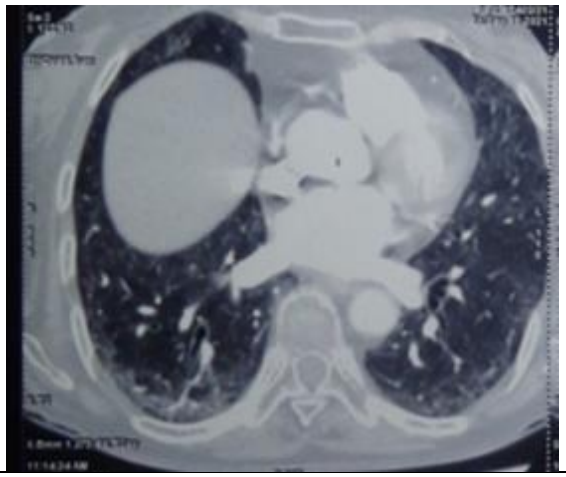


Figure (J) - HRCT scan obtained at six months follow up showing minimal peripherallinear fibrosis with mild ground glass opacity.

Changes of 6-minute walk test.

6MWT was carried out in all the patients of the study group before commencing IV cyclophosphamide therapy. Parameters recorded were the distance walked, pre- and post- oxygen saturation, pulse rate and blood pressure change. At diagnosis, eight patients showed 3-6% drop in saturation while one patient showed 7% drop. At the end of six months of follow-up, all patients had improved 6MWT parameters with only 1-2% drop in saturation **(Figure L).**

Figure K-Changes in the resting oxygen saturation.

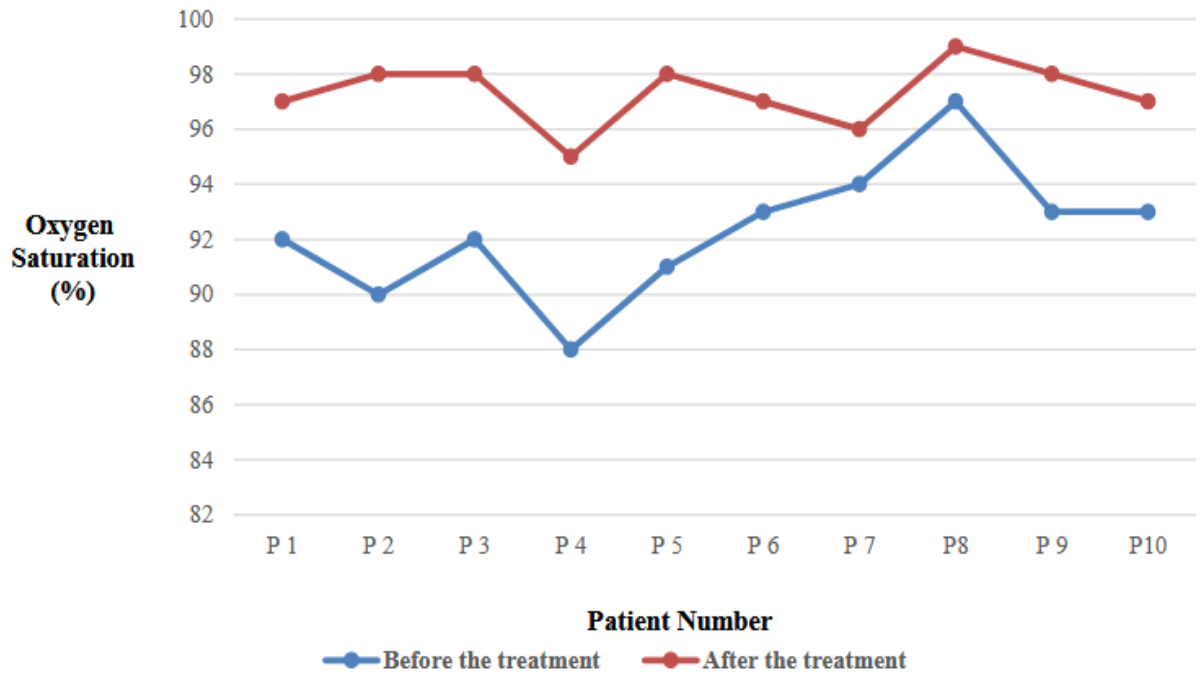
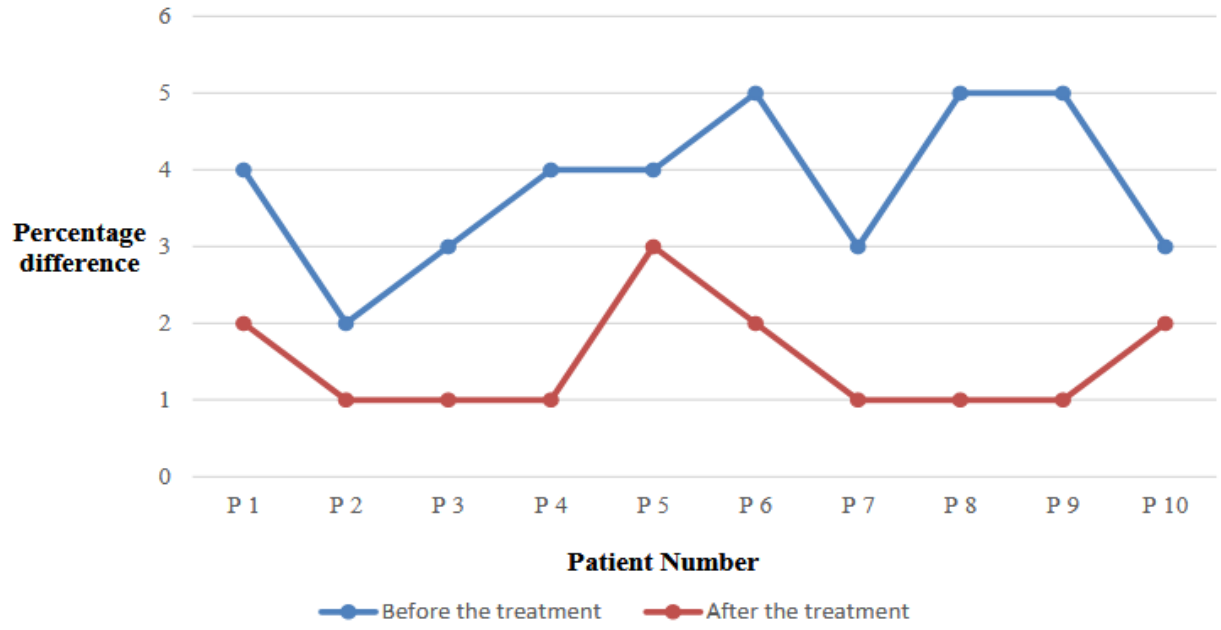


Figure L-Changes in the percentage difference in desaturation.



Changes in Laboratory values during the follow-up period.

Haematological parameters were improved after six months of treatment **(Table 3).**

Variables	Initial (Mean± SD)	6 months (Mean± SD)
White blood cell count	7.414 ±1.969	9.911 ±1.36
Lymphocytes	1.022 ±0.295	2.756 ±0.596
Neutrophils	5.554 ±1.704	6.484 ±0.976
Serum creatinine	123.85 ±26.191	69.37 ±10.771
C-Reactive protein	5.856 ±0.744	1.8515 ±0.738

Discussion.

COVID-19 infection has emerged as a public health emergency with an array of manifestations ranging from asymptomatic infection to life threatening pneumonia [4,5]. Post COVID complications have been reported all over the world with varying severity and multi- organ involvement [5]. One such well recognized pulmonary complication is post-COVID interstitial lung disease, which can lead to progressive respiratory failure requiring respiratory support, including mechanical ventilation [6]. Due to novelty of disease and limited experience associated, up to now there is no definitive treatment for post-COVID ILD [12].

In the context of interstitial lung disease, rapid and effective treatment is important, as delays in treatment may contribute to life-long complications and death [13]. The current standard of practice for COVID associated ILD is steroids. However, a small percentage of patients go on to develop progressive ILD despite being treated with steroid. Therefore, it is important to experiment other drugs with potential benefit for treatment of steroid resistant ILD. In doing so, it is important to select appropriate patients after thorough analysis of clinical symptoms and radiological features. In the current study, we report our unit's experience in using IV cyclophosphamide in confirmed patients with COVID-19-associated ILD, resistant to steroid treatment. Cyclophosphamide is not a commonly used drug in respiratory medicine but is widely used for treatment of various malignant conditions such as lymphoma, breast cancers, ovarian adenocarcinomas, disseminated neuroblastomas, and retinoblastomas [14,15]. It is also an effective immunosuppressive agent, therefore used routinely for treatment of autoimmune diseases such as multiple sclerosis and to prevent

transplant rejections and graft- vs-host complications [16]. One advantage of cyclophosphamide over other immunosuppressant agents is its rapid onset of action and side effect profile [17].
Cyclophosphamide is often administered orally, and the length and the dosage of the treatment depend on the patient factors such as age, body mass, drug interactions and metabolism [18]. There are standard guidelines available regarding proper dosage and indications [18]. Contrary to other studies, IV cyclophosphamide was well tolerated in our patient group and showed better outcomes in clinical status, imaging, spirometry, 6MWT andlaboratory test results [19,20,21].

In post-COVID-19 ILD, a persistent dry cough and worsening or new-onset shortness of breath are frequent presentations [1]. Our study findings revealed shortness of breath, cough, wheezing, and arthralgia/myalgia as the presenting symptoms. Clinical assessment after six months identified a significant improvement in these symptoms. The clinical improvement was also reflected in imaging, with a radiological resolution of the inflammatory changes.
Before commencing IV cyclophosphamide therapy, different pathological patterns were observed in the initial HRCTs of the patients. All the patients had bilateral interstitial abnormalities, and majority had symmetrically distributed HRCT changes with multizonal involvement. Park et al[22] reported that they observed bilateral patchy areas of ground-glass attenuation present alone or with areas of consolidation or irregular lines as the common HRCT finding of seven patients with NSIP [22]. In line with them, we also found ground- glass opacity as the predominant interstitial abnormality in the majority. Areas of consolidation were distributed in both the central and peripheral lung fields. Corte et al[21] carried out a study using IV cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia and reported stable pulmonary functions during six months of follow- up. They reported a greater therapeutic response in HRCT abnormalities suggestive of organized pneumonia [21]. Conforming their findings, we also observed that the interstitial abnormalities of ground-glass attenuation on initial HRCT scans entirely resolved after the treatment. In our study group, a near-complete resolution was observed in initial linear fibrosis, mosaic appearance, and midzonal crazy paving patterns. Moreover, areas of consolidation were cleared with residual minimal bronchiectasis.

The current study has several limitations. This is not a randomized control trial and had a small sample size; therefore, the effectiveness of IV cyclophosphamide therapy could not be precisely measured. It could also be argued that it is not feasible and acceptable to conduct a randomized controlled study on patients with severe progressive ILD, and this may require further discussion. Also, diffusing capacity of the lungs for carbon monoxide (DLCO) measurement as part of pulmonary function testing could not be performed consistently due to unavailability, hence was not included in the study.

Conclusion

IV cyclophosphamide is well tolerated in post-COVID ILD patients with severe and progressive disease. It can be effectively used for treatment of severe progressive COVID-19- related ILD resistant to steroid therapy. However, large scale prospective studies would be needed to determine the precise role of this therapy in COVID related ILD.

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