Descriptive Analysis of the Patients with Post COVID Interstitial Lung Diseases in A Resource-Poor Setting of Central Sri Lanka

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Abstract

Background

To date, COVID-19 continues to remain at pandemic proportions. As of March 2022, COVID-19 has caused over 433 million infections and over 5.9 million deaths around the world. Long COVID associated complications were reported worldwide. COVID associated interstitial lung disease (ILD) is a well-known, recognized long term consequence.

Methodology

A single centre observational study was carried out in the Respiratory Disease Treatment Unit two at National Hospital Kandy, Sri Lanka. Information regarding demographic, clinical, biochemical and radiographic characteristics were extracted from the medical records. An interviewer-administered questionnaire was used. Statistical analysis was performed using IBM SPSS statistics data editor.

Results

53 (13.6%) COVID-19 related ILD cases were analysed. Out of them, 38 (71.7%) were males. The median age was 59 years. The majority of patients (81.1%) provided a history of at least one underlying comorbid disease, of which Diabetes Mellitus was the commonest (58.4%). Out of the male patients, 17 (47.3%) had a positive smoking history of varying pack years. Different pathological patterns, geographical and zonal distributions, occasionally asymmetrical patterns were observed in HRCT of patients with COVID-19 related ILD.

Conclusion

The majority of the COVID-19 related ILD patients were males with multiple comorbidities and had a positive smoking history. HRCT imaging, CXR findings and inflammatory markers are crucial in identifying the progression of the disease. Detection of these findings should alert the clinicians to provide prompt and optimized care in order to minimize the morbidity and mortality of COVID-19 related ILD.
Key words: *COVID-19, Coronavirus disease, interstitial lung disease, Sri Lanka*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS –CoV- 2) or Novel Coronavirus is the causative organism for the COVID-19 pandemic which was first identified in Wuhan, China, in 2019 [1]. As of March 2022, COVID-19 has caused over 433 million infections and over 5.9 million deaths around the world [2]. By March 1st, 2022, more than 0.6 million confirmed cases and 16244 deaths were announced by the Health Ministry of Sri Lanka [3].

There is increasing evidence worldwide of 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 [6]. As there is a scarcity of publications locally describing the

demographical, clinical, and radiographical characteristics of the patients with COVID-19 related ILD, our endeavour was to fill the vacuum of the studies.

Material and methods.

A single-centre 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. Demographic, clinical, biochemical and radiographical data were collected from patients who presented with COVID-19 related ILD, using existing medical records as well as MMRC dyspnoea scale through an interviewer-administered questionnaire. **Inclusion Criteria**: (1) Patients ≥ 18 years (2) Confirmed infection with SARS COVID -2. **Exclusion Criteria**: (1) Patients who are < 18 years (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.

All the patients were examined by an expert respiratory team which comprised respiratory consultants. Follow up imaging was performed using Chest X-Ray and HRCT chest which was jointly interpreted by a consultant respiratory physician and radiologist. Detailed lung function testing including a 6-minute walk test was performed. Six-minute walk tests were carried out at the 1st visit and followed up by trained physiotherapists to assess the functional respiratory status of the patients. Data analysis was carried out by using the IBM SPSS version 25.00 statistics data editor. The data were presented by using descriptive statistics .

Results

A total of 387 COVID-19 confirmed patients were admitted of which, 53 (13.6%) post COVID ILD patients were diagnosed. Out of them, the majority 38 (71.7%) were males. The mean age value of the study cohort was 59 years ranging from 27 to 80 years. A little more than half of the patients, 27 (50.9%) were in the age group of 41-60 years (Table 1).

Table 1- Age distribution of patients with COVID-19 related ILD

Age category	Frequency	Percentage(N=53)
01-20	1	1.9
21-40	4	7.5
41-60	27	50.9
61-80	21	39.6

Out of the male patients, 17 (47.3%) had a positive smoking history of which nine (23.6 %) patients were current and eight (21%) were ex-smokers. The majority, 43 (81.1%), of patients had a history of at least one comorbidity. Diabetes Mellitus(DM) was the commonest comorbidity which accounted for 31 (58.4%), followed by Hypertension 25 (47.2%), Dyslipidaemia 6 (11.3%) and Bronchial Asthma 3 (5.6%) (Table 2). Two comorbidities were found in 19 (35.8%) of the diseased patients, namely Hypertension and Diabetes Mellitus. Three comorbidities were found in two (3.8%) which included Asthma in addition to Hypertension and Diabetes Mellitus.

Table 2: Underlying comorbidities of patients with post COVID-19 ILD.

Underlying Comorbidity	**Frequency**	**Percentage (N=53)**
Diabetes Mellitus	31	58.4
Hypertension	25	47.2
Dyslipidemia	5	11.3
Bronchial asthma	3	5.6
Ischemic heart disease	4	7.9
COPD	2	3.8
Chronic kidney disease	2	3.8

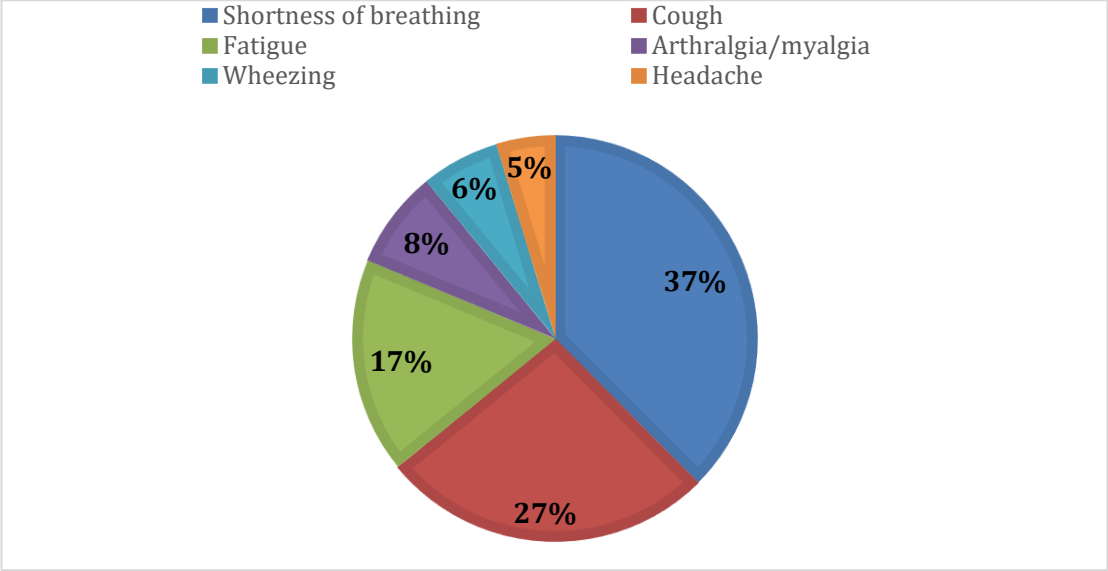
Definition of abbreviations- COPD: Chronic obstructive pulmonary disease

Multiple symptoms were observed in the majority of COVID-19 patients at the time of admission. The most common presenting symptom was shortness of breath, which accounted for 34 (64.2%) patients. Table 3 summarizes the commonly observed symptoms of the patients diagnosed with COVID-19 related ILD. Furthermore, the post COVID symptoms were observed at the 3 months follow-up including shortness of breathing 24 (45.2%), cough 17 (32%), fatigue 11 (20.7%), arthralgia/myalgia 5 (9.4%), wheezing 4 (7.5%) and headache 3 (5.6%) (Figure 1).

Table 3: Presenting symptoms of the patients with post-COVID ILD.

Symptoms	Frequency	Percentage
Arthralgia/ myalgia	7	13.2
Anosmia	2	3.8
Dry cough	26	49.1
Productive cough	11	20.8
Fever	20	37.7
Headache	6	11.3
Loss of appetite	9	17
Sore throat	3	5.7
Shortness of breathing	34	64.2
Wheezing	5	9.4

Figure 1: Post COVID symptoms of the patients



Laboratory abnormalities were summarized in table 4.

Table 4: Laboratory values (Inflammatory markers) of the patients with COVID-19 related ILD.

Variables	At diagnosis	Follow-up
C-reactive protein (mg/mL; normal range ≤ 10.0)	49.2±60.2	6.8±9.8
Lymphocyte count (×109/L; normal range 1.1–3.2)	0.8±0.2	2.6±1.4
Serum creatinine (µmol/L; normal range 41–81)	160.4±32.4	48.7±41.8

-Data are presented as mean ± standard deviation.

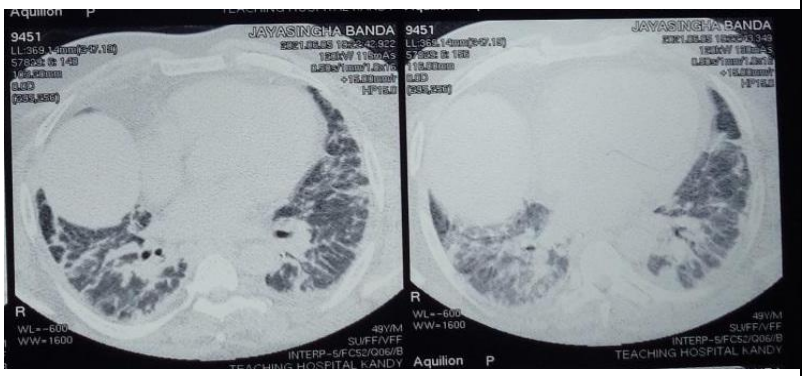
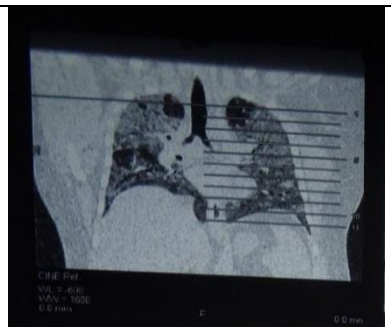
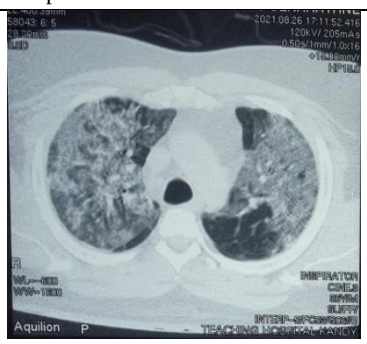
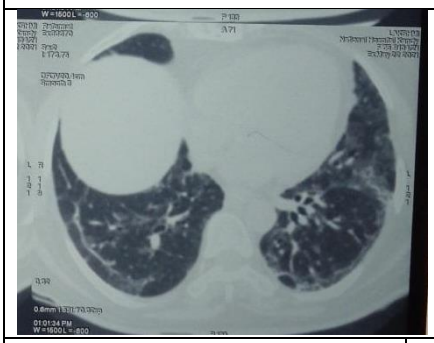
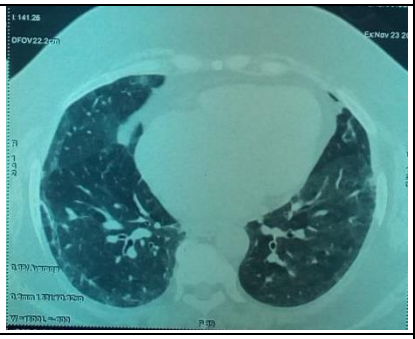
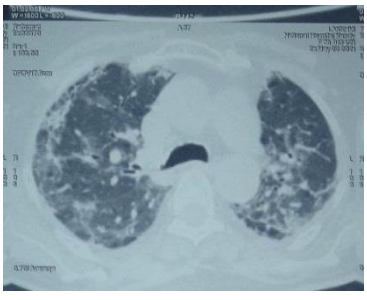
During the first 7-12 days after recovery, abnormalities were observed on chest X-ray including bilateral patchy shadows 31 (60.3%), ground glass opacity 24 (45.2%), local patchy shadows 21 (39.6%), bilateral honeycombing 5 (9.4%), bilateral haziness 3 (5.6%), and COVID BOOP 1 (1.8%) (Bronchiolitis obliterans organizing pneumonia). Table 4 illustrates the HRCT findings of the patients diagnosed with post-COVID ILD.

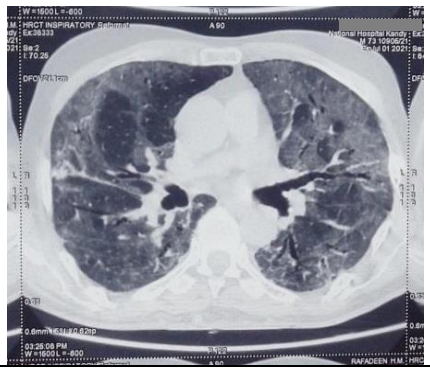
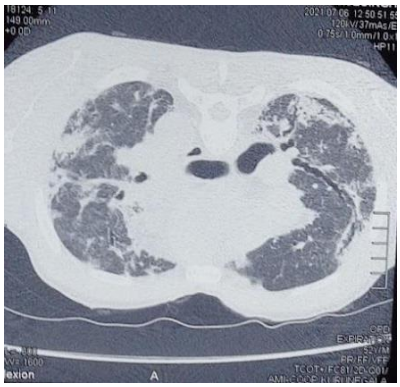
Variables		Frequency (N=53)	Percentage (N=53)
Distribution of Interstitial abnormalities	Asymmetrical	3	5.6%
	Symmetrical	50	94.3%
Geographical distribution	Patchy	2	3.7%
	Generalized	49	92.4%
	Peripheral	51	96.2%
	Central	10	18.8%
	Posterior	47	88.6%
	Lower lobe	14	26.4%
Zonal distribution	Apico basal involvement	42	79.2%
	Lower to mid	11	20.7%
	Upper to mid	4	7.5%
Pathological Appearance	Ground glass opacity	50	94.3%
	Fibrosis	52	98.1%
	Honey comb	3	5.6%
	Linear fibrosis	17	32.0%
	Linear atelectasis	4	7.5%
	Mosaic	7	13.2%
	Crazy paving	9	16.9%
	Traction bronchiectasis	22	41.5%
Standard Pattern	UIP- Definite Problem	1	1.8%
	NSIP- Definite Problem	13	24.5%
	Organizing pneumonia	1	1.8%
	Mixed	36	67.9%
	DIP- Definite Problem	2	3.7%

Table 4- HRCT findings of the patients diagnosed with COVID-19 related ILD.

Definition of abbreviations- UIP: Usual interstitial pneumonia, NSIP: Nonspecific interstitial pneumonia, DIP: Desquamative interstitial pneumonia

HRCT images of the patients with COVID-19 related ILD

Symmetrical Distribution	Ground Glass Opacity
	
Asymmetrical Distribution	Mosaic appearance
 	
Apico basal Involvement	Peripheral to Central distribution
 	
Linear Fibrosis	Ground Glass Appearance with Peripheral Fibrosis
 	
Peripheral Distribution / Generalized Distribution	Crazy Paving appearance

		
Diffuse Distribution	Predominantly peripheral with ground glass appearance	Traction bronchiectasis
		

Six-minute walk test results

The highest percentage difference of desaturation was 6-10% (Table 5). Of the total 53, five patients were unable to perform the test due to medical conditions.

Table 5: Six-minute walk test results of the patients with COVID-19 related ILD

Percentage difference of desaturation	Number of patients
0-2%	3
2-4%	7
4-6%	14
6-10%	23
>10%	1
The distance walked	
50-100m	3
100-150m	3
150-200m	5
200-250m	7
250-300m	10
300-350m	14
350-400m	4
400-450m	2

Discussion

This descriptive analysis explored the demographical, clinical, biochemical and radiographical characteristics of the patients with post-COVID interstitial lung disease in a single tertiary care centre in Sri Lanka. It was found that COVID-19 patients in the age range of 41-60 years were mostly affected with COVID-19 related ILD. In the present study, the median age value of the patients was 59 years. Consistent with recent literature, male predominance was observed in our study as well. Compared to non-

smokers, smokers were 1.4 times more likely to have severe COVID-19 symptoms, 2.4 times more likely to require ICU admission, mechanical ventilation, and to die [7]. Smoking is a contributing factor to the progression of COVID-19 related ILD [7]. Based on our data, 47.3% of the male patients had a positive smoking history.

In this study, more than three fourth (81.1%) of the patients had at least one underlying comorbidity. This is consistent with the published literature [6,8]. The present study found that Diabetes Mellitus was the commonest comorbidity followed by hypertension and bronchial asthma. However, other studies reported hypertension as the commonest comorbidity [9]. A German study, conducted to investigate the incidence of restrictive lung disease and ILD in patients with prediabetes and type 2 DM reported increased risk for dyspnoea and ILD in patients with type 2 DM [10]. When comparing patients with long-term type 2 diabetes to patients with pre-diabetes and non-diabetics on the mMRC (Modified medical research council) dyspnoea scale, patients with long-term type 2 diabetes had increased breathlessness [10]. These findings highlight the necessity of immediate screening for comorbidities. However, further studies need to be conducted with large cohorts to explore the association between Diabetes mellitus and increased risk for post-COVID ILD.
At the diagnosis of COVID-19 related ILD, diseased patients had abnormal biochemical and haematological investigations, in particular Lymphocyte count, CRP, and serum creatinine. However, at follow-up, biochemical markers indicated an improvement in systemic inflammation. Which is parallel with the reported literature [6].

In our study, presenting symptoms of the patients who were diagnosed with COVID-19 related ILD are arthralgia/ myalgia, anosmia, dry cough, productive cough, fever, headache, loss of appetite, sore throat, shortness of breathing, and wheezing. These symptoms were presented within 7-12 days after the recovery of acute COVID infection. During the follow-up visits, the majority of the patients were presented with post COVID symptoms including shortness of breath, cough, fatigue, arthralgia/myalgia, wheezing, and headache. Similar to our findings, Jessica González and colleagues found dyspnoea, muscular fatigue and wet and dry cough as the symptoms at the 3 months follow-up of their cohort [11].

HRCT is an effective method to detect the progression of viral pneumonia and to classify the severity of the disease [12]. We have observed different pathological patterns, geographical and zonal distributions, occasionally asymmetrical patterns in HRCT of patients with COVID-19 related ILD. In our patients, the majority had a symmetrical distribution in HRCT which tallies with normal ILD entity. However, three patients had asymmetrical distribution. More than 80% of the patients were reported with generalized, peripheral and posterior geographical distributions. The majority of the cases had multiple zonal involvements, where the highest was noted as apicobasal distribution. Furthermore, lower to mid and upper to mid distributions were reported. Fibrosis was the most common pathological appearance followed by Ground Glass Opacity, Traction bronchiectasis, Linear fibrosis, Crazy paving, Mosaic, and Linear atelectasis. Similar to our findings, other studies also reported HRCT abnormalities including ground-glass opacities, consolidations, crazy-paving pattern, and linear opacities, primarily affecting peripheral areas [13,14], lower lobes and displaying a multilobar distribution [5,6]. More than half of the patients were reported with a mixed standard pattern. Moreover, definite cases of NSIP, DIP, UIP and Organizing pneumonia were observed respectively.

In the present study, the main X-Ray findings of the initial phase of post-COVID-ILD were bilateral patchy shadows, ground-glass opacity, and local patchy shadows. However, chest X-rays could be used as an alternative radiological investigation method in patients with COVID-19[15].At the 6-minute walk test, most of the patients had a 6-10% difference of desaturation with the highest distance walked being 300-350m. This is consistent with previous studies [6,11].

Conclusion

This study reveals that males with multiple comorbidities and smoking history are at a higher risk of being a victim of COVID-19 related ILD. These findings should alert the clinicians to provide prompt and optimized

care in order to minimize the long-term complications of post-COVID ILD. The main limitation of this study was the small sample size. Hence, we recommend multicentre studies with a large cohort.

Conflict of interest

There is no financial interest or any conflict of interest related to this paper.

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