Original article

DESCRIPTIVE ANALYSIS OF THE PATIENTS WITH POST COVID INTERSTITIAL LUNG DISEASES IN A TERTIARY CARE HOSPITAL IN CENTRAL SRI LANKA: AN OBSERVATIONAL STUDY

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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 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 radio graphical characteristics were extracted from the medical records. An interviewer-administered questionnaire was used. Statistical analysis was performed using IBM SPSS statistics data editor.

Results: A total of 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%) were given a history of at least one underlying comorbid disease, while 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. The progression of the disease is well displayed in the findings of HRCT. 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, interstitial lung disease, Sri Lanka

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS –CoV- 2) or Novel Coronavirus is the causative organism for the coronavirus disease 2019 (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]

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There is increasing evidence worldwide with 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] According to the world health organization, post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually three months from the onset of COVID-19 with symptoms and that last for at least two months and cannot be explained by an alternative diagnosis.[7] ILD has a significant link with the viral pneumonia such as coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 and is characterized by the progressive scaring of the lung tissue, impaired lung function, and impaired gas exchange.[8] As there is a scarcity of publications locally describing the demographical, clinical, and radio graphical characteristics (Appendix 1) of the patients with COVID-19 related ILD, our endeavour was to fill the vacuum of the studies.

Appendix 1	
Radio graphical characteristics	**Definition**
Honey combing	Presence of small cystic spaces lined by bronchiolar epithelium with thickened walls composed of dense fibrous tissue.
Ground glass opacity	Filling of the alveolar spaces with pus, edema, hemorrhage, inflammation or tumor cells. Thickening of the interstitium or alveolar walls below the spatial resolution of the HRCT.
Fibrosis	Term given when there is an excess of fibrotic tissue in the lung. It can occur in a wide range of clinical settings and can be precipitated by a multitude of causes.
Crazy paving	Crazy Paving is a combination of ground glass opacity with superimposed septal thickening.
Mosaic attenuation	Density differences between affected and non-affected lung areas. There are patchy areas of black and white lung.
Linear atelectasis	Focal area of subsegmental atelectasis with a linear shape. It is normally horizontal and sometimes oblique or perpendicular.
Traction bronchiectasis	Irreversible dilation of the bronchi resulting from airway damage due to a variety of causes, including infection, airway obstruction, or fibrosis.
UIP- Usual interstitial pneumonia	Morphologic entity defined by a combination of (1) patchy interstitial fibrosis with alternating areas of normal lung, (2) temporal heterogeneity of fibrosis characterized by scattered fibroblastic foci in the background of dense acellular collagen, and (3) architectural alteration due to chronic scarring or honeycomb change.
NSIP- Nonspecific interstitial pneumonia	Chronic interstitial pneumonia with the homogeneous appearance of interstitial fibrosis and inflammation.
DIP- Desquamative interstitial pneumonia	Accumulation of numerous pigmented macrophages within most of the distal airspace of the lung and, sometimes, the presence of giant cells.

Material and methods

An observational study was carried out in the Respiratory Disease Treatment Unit two at National Hospital Kandy (NHK), Sri Lanka between 6th January 2021 to 12th January 2022. This is a training and research unit which carries out programmes for medical students and post-graduate students with the diploma in tuberculosis and chest diseases (DTCD). This is the second biggest unit in NHK, headed by the consultant respiratory physician.

The inclusion and exclusion criteria are:

Inclusion Criteria: (1) Patients ≥ 18 years (2) Confirmed infection with SARS COVID-2 (3) Confirmed post COVID-ILD within 6-20 weeks (Mean ± SD = 12.1 ±1.1) following the acute 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.

SARS COVID-2 cases were defined as a positive result by using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) detection on a nasopharyngeal swab. Demographic, clinical, biochemical and radio graphical data were collected from patients who presented with COVID-19 related ILD, using existing medical records through a questionnaire consisted of necessary retrospective information.

COVID associated ILD was diagnosed in patients who developed persistent or worsening respiratory symptoms and High-Resolution Computer Tomography (HRCT) features favouring ILD pattern at least 6 weeks following the acute COVID infection. Spirometry and Six-minute walk test data were collected from patients who were diagnosed with COVID-19 associated ILD, using existing medical records.

All patients were examined by an expert respiratory team led by respiratory consultants. Imaging such as Chest X-Ray and HRCT chest were jointly interpreted by a consultant respiratory physician and a radiologist. Ethical clearance was obtained from the ethics review committee of NHK. Data analysis was carried out using the IBM SPSS version 25. The data were presented using descriptive statics in the form of frequency, percentage and mean.

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, majority 38 (71.7%) were males. The mean age of the study cohort was 59± 11.21 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 (n=53)

Age category	Frequency	Percentage
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 9 (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 was the commonest comorbidity which accounts for 31 (58.4%), followed by Hypertension 25 (47.2%), Dyslipidaemia 6 (11.3%) and Bronchial Asthma 3 (5.6%) **(Table 2)**. Two comorbidities (Hypertension and Diabetes Mellitus) were found in 19 (35.8%) of the diseased patients. Three comorbidities (hypertension, diabetes mellitus, asthma) were found in 2 (3.8%) of the patients.

Table 2: Underlying comorbidities of patients with post COVID-19 ILD (n=53)

Underlying Comorbidity	Frequency	Percentage
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

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 account for 34 (64.2%) patients. **Table 3** summarizes the commonly observed initial symptoms of the patients diagnosed with COVID-19 related ILD. Furthermore, the post COVID symptoms have observed existentially at the three 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)**.

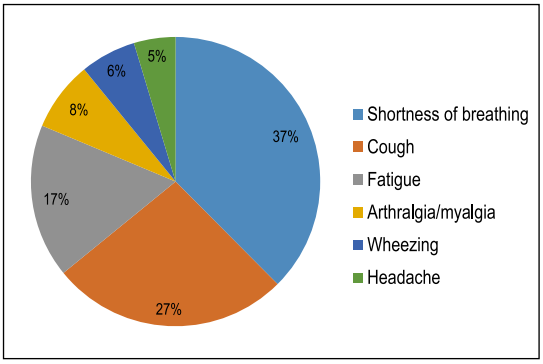


Figure 1: Post COVID symptoms of the patients at the 3 months follow-up (n=53)

Table 3: Presenting symptoms of the patients with post-COVID ILD (n=53)

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

During the first 15-30 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 secondary organizing pneumonia due to COVID-19 1 (1.8%).

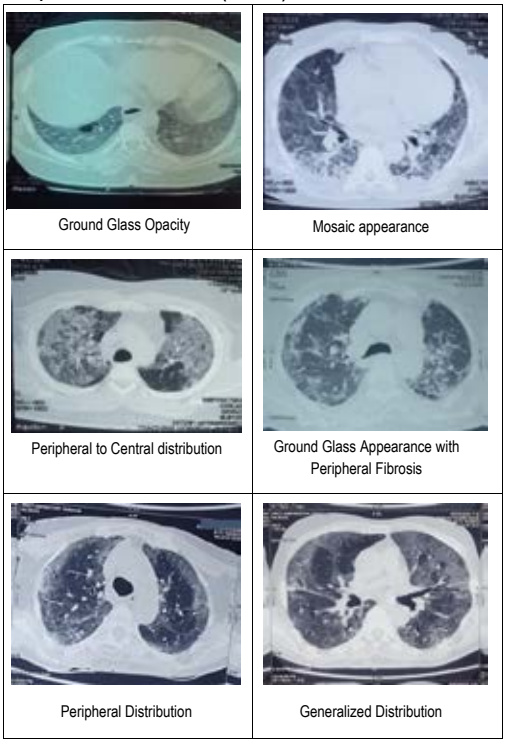
Table 4 illustrates the HRCT findings of the patients diagnosed with post-COVID ILD

Table 4- HRCT findings of the patients diagnosed with COVID-19 related ILD (n=53)

Variables		Frequency	Percentage
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 combing	3	5.6
	Linear fibrosis	17	32.0
	Linear atelectasis	4	7.5
	Mosaic attenuation	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

Definition of abbreviations- UIP: Usual Interstitial Pneumonia, **NSIP:** Nonspecific Interstitial Pneumonia, **DIP:** Desquamative Interstitial Pneumonia

Table 5- HRCT images of the patients diagnosed with post-COVID ILD (n=14)



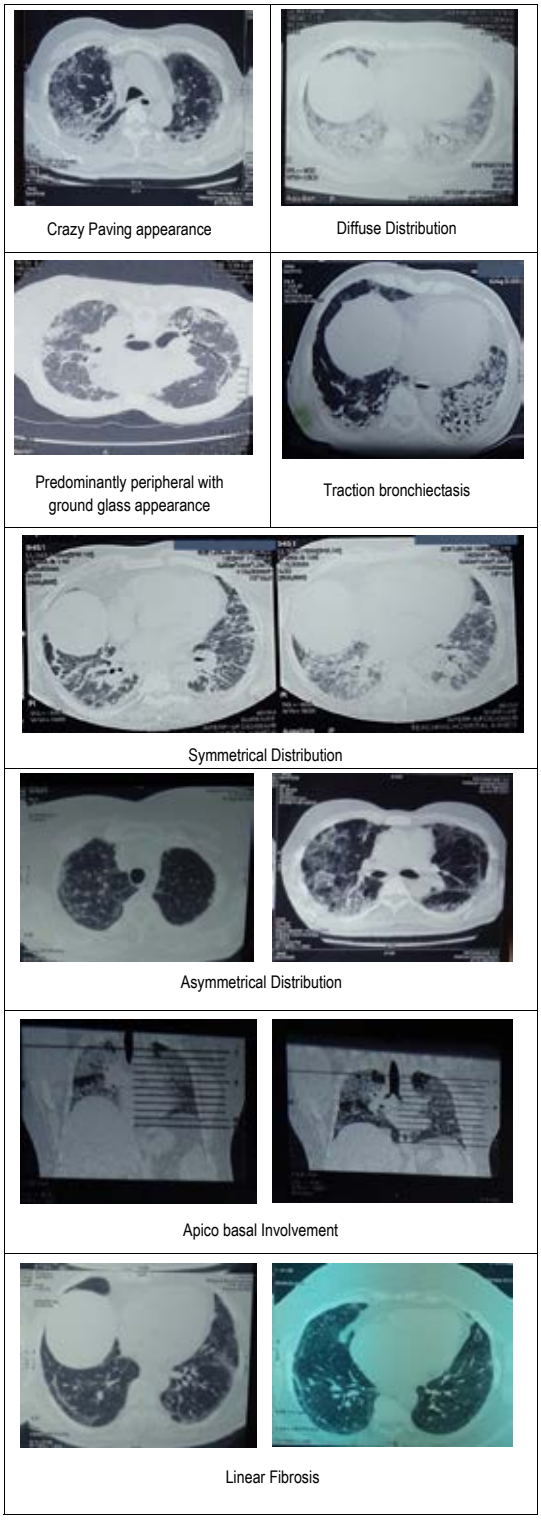


Table 6 illustrates the spirometry values at the initial diagnosis of post COVID-ILD. Three patients were unable to perform spirometry due to the worsening of breathlessness and fatigue.

Table 6: Spirometry values of the patients with COVID-19 related ILD (n=50)	
Descriptive statistics	Mean ± (SD) (N=50)
FVC (Pred)	1.74 ± 0.86
FEV1 (Pred)	1.49 ± 0.65
FEV1/FVC (%)	88.28 ± 17.9

Definition of abbreviations-FVC: Forced Cital Capacity, **FEV1:** Forced Expiratory Volume

Six-minute walk test results

At the diagnosis of the COVID-19 related ILD, the basic six-minute walk test was performed with the supplemental oxygen by measuring pre and post oxygen saturation, pulse rate and blood pressure changes. However, complete information was lacking at the time of analysis. The highest percentage difference of desaturation was 6-10%. **(Table 7)** Test was prematurely stopped due to worsening of breathlessness and general fatigue in five patients.

Table 7: Six-minute walk test results of the patients with COVID-19 related ILD (n=48)	
Percentage difference of desaturation	Number of patients
0-2% 2-4% 4-6% 6-10% >10%	3 7 14 23 1
The distance walked	
50-100m 100-150m 150-200m 200-250m 250-300m 300-350m 350-400m 400-450m	3 3 5 7 10 14 4 2

DISCUSSION

This descriptive analysis explored the demographical, clinical, biochemical and radio graphical characteristics of the patients with post-COVID interstitial lung disease in a single tertiary care center in Sri Lanka. It was found

that the COVID-19 patients in the age group of 41-60 years had the highest proportion to be a victim of COVID-19 related ILD. In the present study, the median age value of the diseased was 59 years. Consistent with recent literature, male predominance was observed in our study. Compared to nonsmokers, 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 [9]. Smoking is a contributing factor to the progression of COVID-19 related ILD.[9] 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 diseased patients had at least one underlying comorbidity. This is consistent with the published literature.[6,10] 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.[11] González et al. (2021) conducted to investigate the incidence of restrictive lung disease and ILD in patients with pre-diabetes and type 2 DM reported increased risk for dyspnoea and ILD in patients with type 2 DM (Diabetes Mellitus).[12] 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.[12,13] 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 the 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 15-30 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.[12]

HRCT is an effective method to detect the progression of viral pneumonia and to classify the severity of the disease.[14] 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[15,16] 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.[17] 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. [6,13]

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. 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

None

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