COVID-19 Associated Interstitial Lung Disease - An Emerging Entity

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Research article

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Abstract

**Background:** COVID-19 disease associated pulmonary sequelae has been increasingly reported after recovery from acute infection. Therefore, we aim to explore the characteristics of interstitial lung disease in patients with COVID-19.

**Methods:** An observational study was conducted in patients with COVID-19 associated ILD from April 2020 till September 2020. Patients ≥18 years of age with COVID-19 who were diagnosed with ILD based on respiratory symptoms and HRCT chest imaging after the recovery phase of COVID-19 infection were recruited. Data was recorded on a structured proforma, and descriptive analysis was performed using Stata version 12.1.

**Results:** A total of 30 patients with COVID-associated ILD were identified. The mean age of patients was 59.14 (SD 12.60) and 27 (90%) were males. Four HRCT patterns of interstitial lung disease were seen; organizing pneumonia in 10 (33.33%), non-specific interstitial pneumonitis in 17 (56.67%), usual interstitial pneumonitis in 12 (40%) and probable usual interstitial pneumonitis in 14 (46.67%). Diffuse involvement was found in 15 (50%) patients, while peripheral predominance in 15 (50%) and other significant findings were seen in 8 (26.67%) patients. All patients were treated with corticosteroids. The case fatality rate was 16.67%. Amongst the survivors, 8 (32%) recovered completely, 9 (36%) improved, while 8 (32%) patients had static or progressive disease.

**Conclusions:** This is the first study from Southeast Asia that identified COVID-associated interstitial lung disease in patients who had no pre-existing lung disease, highlighting the importance of timely recognition and treatment of an entity that might lead to fatal outcome.

**Background**

The Coronavirus disease (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a global economic, psychosocial, political and medical challenge. As patients recover from COVID-19 disease, we are approaching an era where physicians would encounter COVID associated pulmonary sequelae. These could be infectious, like COVID associated pulmonary aspergillosis (CAPA) [1]; or non-infectious which could include COVID associated interstitial lung disease (ILD), an increasingly recognized entity. The previous epidemics of coronavirus due to severe acute respiratory distress syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) also led to the development pulmonary fibrosis [2, 3].

ILD covers a wide spectrum of pulmonary parenchymal disorders of both known and unknown etiology. Different radiological and histopathologic patterns of ILD have been described, some of which include usual interstitial pneumonitis (UIP), nonspecific interstitial pneumonitis (NSIP), and organizing pneumonia (OP) [4]. Similar patterns can also occur as a result of pulmonary infections, like pneumocystis pneumonia or cytomegalovirus pneumonitis [5, 6].
The diagnosis of ILD during COVID-19 pandemic remains challenging because invasive testing like bronchoscopies, open lung biopsies, or autopsies are rarely performed in COVID-19 patients due to risk of disease transmission. Although there are multiple reports on the importance of CT in diagnosing COVID-19 infection, there is little or no data on the clinical presentation and management of patients with ILD associated with COVID-19.

Some patients after recovery from COVID-19 infection might present with new, persistent or worsening respiratory symptoms due to COVID-19 associated Interstitial Lung disease. Our study aims to describe this underdiagnosed entity and underscore the importance of appropriate follow-up and prompt diagnosis of these patients, to facilitate early management and prevent fatal outcomes.

**Methods**

**Study Design and Setting:**

This single-center observational study was performed between April 1, 2020 and September 15, 2020 at the Aga Khan University Hospital, the largest tertiary care center located in Karachi, Pakistan. We retrospectively collected the demographic, clinical, laboratory and radiological data of patients presenting with COVID-19 associated ILD from medical records. Disease severity of patients with COVID-19 infection was classified according to the WHO classification[7]. High resolution computed tomography (HRCT) of the chest findings, treatment and outcomes were recorded.

**Study Subjects:**

Patients who were seen in the outpatient Pulmonology clinic or inpatient consultation service at the Aga Khan University Hospital, owing to persistent respiratory symptoms after recovery from COVID-19 infection, were included in the study. Follow-up imaging with either HRCT or chest X-ray performed 6 to 8 weeks after treatment was interpreted and compared with previous imaging for disease progression, improvement or resolution.

**Proposed Diagnostic Criteria for COVID-19 associated ILD (COVILD):**

The COVILD diagnosis in our study was based on ‘new, persistence and/or worsening of respiratory symptoms and identification of ILD pattern on HRCT imaging of the chest after the initial recovery phase of acute COVID-19 infection defined as 6 to 8 weeks after the onset of infection with no previous history of ILD. They were diagnosed to have ILD by a specialist in the ILD clinic or on inpatient consultation’.

**Inclusion and Exclusion Criteria:**

Adult patients (age 18 and above) who were confirmed for SARS-CoV-2 by nasopharyngeal and/or oropharyngeal swabs for real-time RT-PCR at initial presentation and underwent HRCT on follow-up visit
were included in our study. Patients with pre-existing ILD and those with incomplete medical records were excluded.

**Operational Definition of Outcomes:**

We have defined outcomes as complete recovery, improvement and progression of the disease process. Patients were labelled as completely recovered if they returned to their baseline functional status and chest imaging showed clearance of lung infiltrates after the diagnosis of COVID-19 associated ILD. Improvement was defined as subjective improvement in functional status but not to the baseline and at least 50% clearance of radiological infiltrates. The patients whose symptoms persisted with interval worsening of functional status and no significant improvement or had worsening of lung infiltrates had progression of the disease process.

**HRCT Chest Analysis:**

The key HRCT chest findings of COVID-associated ILD were defined using standard taxonomy described in the ILD literature with interstitial patterns including but not limited to diffuse ground glass opacities (GGOs) with or without traction bronchiectasis (NSIP), basal and peripheral opacities with honey combing (UIP) and peripheral and peribronchovascular consolidation with or without ground-glass opacities (OP) [8]. The main HRCT findings were described as GGOs, consolidation, honeycombing/fibrosis and interlobular septal thickening/reticulation. Other HRCT findings included crazy paving, reverse halo sign, traction bronchiectasis and emphysematous cysts. The distribution of pulmonary involvement was reported as either peripheral or diffuse.

**Statistical Analysis:**

Statistical analyses were performed using Stata version 12.1. Quantitative data were presented as mean ± standard deviation (SD), while frequencies and percentages were used to represent qualitative (categorical) data. The $P$ value < 0.05 was considered statistically significant.

**Results**

As shown in Table 1, our cohort included 30 patients, 27 were males (90%) with an average age of 59.14 ± 12.60 years. Common presenting symptoms of COVID-19 disease were fever (30, 100%), cough (19, 63.33%) and shortness of breath (23, 76.67%). During initial COVID-19 disease, 13 (43.33%) patients had moderate disease, 13 (43.33%) patients had severe disease, and 4 (13.33%) had critical disease. Out of the 30 patients, 26 (86.67%) patients required supplemental oxygen, 12 (40%) were treated with non-invasive ventilation (NIV) while 2 (6.67%) patients were treated with invasive mechanical ventilation.
# Table 1
Clinical and Demographic Characteristics of patients with COVID associated ILD ($n = 30$)

| Variables                                      | Findings             |
|------------------------------------------------|-----------------------|
| **Age (Years, Mean ± SD)**                     | 59.14 ± 12.604        |
| **Gender no. (%)**                             |                       |
| Male                                           | 27 (90)               |
| Female                                         | 3 (10)                |
| **Comorbidities no. (%)**                      |                       |
| Diabetes Mellitus                              | 14 (46.66)            |
| Hypertension                                   | 13 (43.33)            |
| Chronic Obstructive Pulmonary Disease          | 1 (3.33)              |
| Chronic Liver Disease                          | 1 (3.33)              |
| Malignancy                                     | 1 (3.33)              |
| Ischemic Heart Disease                         | 1 (3.33)              |
| Inflammatory Bowel Disease                     | 1 (3.33)              |
| Chronic Kidney Disease                         | 1 (3.33)              |
| **Smoking no. (%)**                            |                       |
| Current Smokers                                | 3 (10)                |
| Ex-smokers                                     | 8 (26.67)             |
| Non-smokers                                    | 19 (63.33)            |
| **Symptoms on Presentation with COVID-19 no. (%)** |                     |
| Fever                                          | 30 (100)              |
| Shortness of Breath                            | 23 (76.67)            |
| Cough                                          | 19 (63.33)            |
| Fatigue                                        | 9 (30)                |
| Headache                                       | 2 (6.67)              |
| **Persistent Respiratory Symptoms no. (%)**    |                       |
| Persistent Cough                               | 13 (43.33)            |
| Persistent Shortness of Breath                 | 29 (96.67)            |
| Variables                                      | Findings            |
|------------------------------------------------|---------------------|
| **Severity of COVID-19 Disease on initial presentation no. (%)** |                     |
| Moderate                                       | 13 (43.33)          |
| Severe                                         | 13 (43.33)          |
| Critical                                       | 4 (13.33)           |
| **Treatment given for COVID-associated ILD no. (%)**  |                     |
| Home Oxygen                                    | 28 (93.33)          |
| Prednisolone                                   | 30 (100)            |
| Pirfenidone                                    | 2 (6.67)            |

**Abbreviations:** COVID-19, Coronavirus Disease 2019; ILD, Interstitial Lung Disease; and SD, Standard Deviation.

All patients in our cohort were found to have bilateral lung disease. Four HRCT patterns of interstitial lung disease were seen (Table 2). Diffuse involvement was found in 15 (50%) patients, while peripheral predominance in 15 (50%) and other significant findings were seen in 8 (26.67%) patients.
Table 2
Radiological patterns of COVID associated ILD (n = 30)

| Variables | Findings |
|-----------|---------|
| **Main Findings no. (%)** | |
| Patchy consolidation with ground glass opacity (OP pattern) | 10 (33.33) |
| Diffuse ground glass opacities (NSIP pattern) | 17 (56.67) |
| Honeycombing/Fibrosis (UIP pattern) | 12 (40) |
| Interlobular Septal Thickening/Reticulation (probable UIP) | 14 (46.67) |
| **Distribution no. (%)** | |
| Peripheral | 15 (50) |
| Diffuse | 15 (50) |
| **Other Findings no. (%)** | |
| Crazy paving | 2 (6.67) |
| Reverse halo sign | 1 (3.33) |
| Traction bronchiectasis | 4 (13.33) |
| Emphysematous cysts | 1 (3.33) |

**Abbreviations:** COVID-19, Coronavirus Disease 2019; ILD, Interstitial Lung Disease; OP, Organizing Pneumonia; NSIP, Nonspecific Interstitial pneumonia; and UIP, Usual Interstitial pneumonia

All patients were treated with corticosteroids (0.5-1 mg/kg/day) for a minimum of 6 to 8 weeks. Home oxygen was needed in 93.33% patients for an average duration of 29 days (mean 29.1 SD 26, median 30). Two patients (6.67%) were treated with pirfenidone for fibrotic lung disease.

Five patients (16.67%) died during the disease course; 4 patients (13.33%) died due to hypoxic respiratory failure, while 1 (3.33%) succumbed to superimposed aspergillus infection (Table 3). Follow-up HRCT scans were performed in 10 patients. The CT images of 3 patients with different patterns of ILD are shown in Fig. 1–3. Others were followed with chest X-rays. Out of the 25 alive patients, 8 (32%) recovered completely, 9 (36%) improved while 8 (32%) patients had static or progressive disease.
Table 3
Outcomes of COVID associated ILD Patients (n = 30)

| Variables                        | Findings |
|----------------------------------|----------|
| Outcomes (n, %)                  |          |
| Alive                            | 25 (83.33) |
| Complete Recovery                | 8 (26.67)  |
| Improvement                      | 9 (30)    |
| Static or Progressive Disease    | 8 (26.67)  |
| Deceased (Cause of Death)        | 5 (16.67)  |
| Hypoxic Respiratory Failure      | 4 (13.33)  |
| Superimposed Infection           | 1 (3.33)   |

Abbreviations: COVID-19, Coronavirus Disease 2019; and ILD, Interstitial Lung Disease

The ILD patterns/features were observed in recovered patients with moderate, severe and critical initial disease, with no significant association of any specific features observed with disease severity (P > 0.05).

**Discussion**

Our study found four distinct patterns of ILD associated with COVID-19 disease. Development of interstitial lung disease amongst survivors of COVID-19 disease has been reported during the ongoing pandemic, however data is limited to case reports [9–11]. Literature from the previous outbreaks of viral infections such as SARS and MERS, in 2002 and 2012 respectively, reported that clinico-radiological changes persisted in approximately one-third of patients even after 12 weeks of discharge [2, 3, 12].

The majority of our patients who developed COVID-associated ILD were males, which has also been previously reported in literature with certain ILDs like idiopathic pulmonary fibrosis [13, 14]. COVID associated fibrosis is one of the lung insults already described with previous Coronavirus infections [2, 3], and there are emerging studies now reporting COVID-19 associated early pulmonary fibrosis. In the initial studies, Pan et al. and Zhou et al. reported fibrotic changes in the imaging features of patients with COVID-19 pneumonia [12, 15]. Since then, fibrotic lung parenchymal remodelling [16, 17], fibrosing diffuse alveolar damage (DAD) [18] and honey combing [19] have also been confirmed after invasive testing such as cryobiopsies and autopsies in smaller cohorts. Li Yan et al. described DAD on autopsy of 30 patients with COVID-19, showing 43% developing fibrosing patterns while 25% showing organizing pattern [6].

Post-infectious secondary OP is a known entity, well described with certain viruses like Cytomegalovirus and Influenza A (H1N1) [6, 20]. Pathology in patients who recovered from SARS-CoV has shown
fibrogranulation tissue proliferation and organizing pneumonia like patterns [21] while MERS associated organizing pneumonia has also been documented [22, 23]. Studies of COVID-19 CT imaging, along with postmortem lung biopsies and autopsies during the ongoing pandemic, suggest the development of a secondary OP, which at present remains an underrecognized complication [24].

A distinct feature of organizing pneumonia and NSIP is the remarkable resolution with corticosteroid treatment. Although the use of corticosteroids has been recommended in the treatment of COVID-19 disease [25], there is limited or no data on response of prolonged or higher dose corticosteroids in COVID-19 associated interstitial lung disease.

In our cohort, most patients developed a predominant OP or NSIP pattern with moderate to severe disease. Most patients with an OP and NSIP pattern improved significantly with steroids, showing both clinical and radiological improvement. UIP pattern however largely remained static or progressed.

Disease severity did not seem to have a significant impact on development of any particular ILD pattern. This proves that these interstitial changes are not only a result of post-ARDS fibrosis or ventilator induced lung damage, but also a consequence of the direct virus induced injury and aberrant local immune response leading to ILD. Combet et al. recently described a case of a spontaneously breathing patient who developed rapid honeycombing following COVID-19 disease which responded to high-dose steroids and nintedanib [26]. Tale et al. also reported a similar case of a patient with persistent hypoxemia after recovery from moderate COVID-19 disease with 3 week follow-up HRCT showing architectural distortion, interlobar septal thickening and traction bronchiectasis [27]. These case reports reiterate our stance that predisposed patients who are moderately ill, and do not require mechanical ventilation can also develop early fibrotic changes. Post-viral pulmonary fibrosis associated with previous corona viruses has been seen in patients with critical disease leading to ARDS with longer duration of illness requiring ICU stay and invasive mechanical ventilation [2]. However, SARS-CoV-2 has shown to induce fibrosis in those patients suffering from moderate disease, which did not require invasive mechanical ventilation or ICU stay in our study.

The strength of our study is that we propose a new working definition of COVID-19 associated ILD (COVILD). To the best of our knowledge this is a first case series emphasizing and presenting a data of 30 patients with different patterns of COVID-19 associated ILD along with their follow up from a low to middle income country.

Our study has several limitations which includes the absence of histopathologic confirmation of ILD. Transbronchial and open lung biopsies were not performed due to the cost, invasive nature of procedure and risk of transmission of COVID-19; therefore our patients were diagnosed solely on clinical and radiological grounds. We did not have follow-up HRCT imaging on all the patients, due to financial constraints. Limited number of pulmonary function tests and diffusion capacity of lung for carbon monoxide (DLCO) were performed to assess the physiologic function of the lung.
Conclusion

COVID-19 associated interstitial lung disease is a new entity. Close follow-up is essential in these patients, as they may require prolonged treatment with corticosteroids. The long-term effect of COVID-associated ILD is yet to be determined, and a longitudinal follow-up will help us further explore the nature of disease.

Abbreviations

COVID-19: Coronavirus Disease 2019, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, CAPA: COVID associated Pulmonary Aspergillosis, ILD: Interstitial Lung Disease, SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus, MERS-CoV: Middle East Respiratory Syndrome Coronavirus, UIP: Usual Interstitial Pneumonia, NSIP: Nonspecific Interstitial Pneumonia, OP: Organizing Pneumonia, ERC: Ethical Review Committee, HRCT: High Resolution Computed Tomography, COVILD: COVID associated Interstitial Lung Disease, GGO: Ground Glass Opacities, SD: Standard Deviation, and DAD: Diffuse Alveolar Disease

Declarations

Ethics approval and consent to participate:

Approval of the Ethical Review Committee (ERC) of the Aga Khan University Hospital located in Karachi, Pakistan was obtained (ERC Reference # 2020-5269-11494) and informed consent requirement was waived because of retrospective nature of the study.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

None.

Authors’ contributions:
ABSZ was responsible for the concept and design of the study. SA analysed the data and oversaw all analyses. ABSZ, AS, SMZ, ASA, SA and MI were responsible for data interpretation and drafting the manuscript. ABSZ, AS, SMZ, ASA, SA and MI revised the manuscript critically for intellectual content. All authors have approved the final version to be published and are jointly accountable for all aspects of the work.

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Figures

Figure 1

CT scan chest of a patient showing a) ground glass opacities (GGOs) consistent with interlobular septal thickening (yellow arrow showing GGOs and septal thickening); and b) interval reduction in GGOs and septal thickening after initiation of corticosteroids.

Figure 2
CT scan chest of a patient showing a) peripheral patchy areas ground glass opacities (GGOs) with consolidation consistent with an OP (organizing pneumonia) pattern (yellow arrow pointing towards peripheral patchy GGOs); and b) complete resolution of peripheral patchy GGOs after initiation of corticosteroids.

**Figure 3**

CT scan chest of a patient showing a) honeycombing and reticulation (yellow arrow showing honeycombing); and b) persistent and worsening of honeycomb fibrosis (yellow arrow showing honeycombing).