Persistent Post-COVID-19 Inflammatory Interstitial Lung Disease: An Observational Study of Corticosteroid Treatment

Katherine Jane Myall (MRCP)[1] ,Bhashkar Mukherjee (PhD) [1], Ana Margarida Castanheira (MSc)[1], Jodie L. Lam (BSc (Hons)[1], Giulia Benedetti (MD)[2], Sze Mun Mak (FRCR)[2], Rebecca Preston (FRCR)[2], Muhunthan Thillai (PhD)[3], Amy Dewar (MRCP),[1] Philip L Molyneaux (PhD)[4&5]and Alex G.West (MRCP)[1]

1. Department of Respiratory Medicine, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London SE1 9RT
2. Department of Radiology, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London SE1 9RT
3. Department of Interstitial Lung Disease, Royal Papworth Hospital NHS Foundation Trust, Cambridge UK
4. National Heart and Lung Institute, Imperial College London, UK
5. Royal Brompton Hospital, UK.

Corresponding Author:
Dr Katherine Myall
Guy's and Saint Thomas' Hospitals NHS Trust - Respiratory Medicine
Great Maze Pond London SE1 9RT
United Kingdom of Great Britain and Northern Ireland
tel: 02071887188 (ext 85834
e-mail: katherine.myall@gstt.nhs.uk

Funding: No funding was received for this research

Author Contributions: KJM, BM, AD, AGW contributed to study design, clinical care, data collection and analysis; AMC contributed to clinical care, data collection; JLL contributed to data collection and analysis; GB, RP and SMM contributed to image acquisition and analysis; PM and MT contributed to data interpretation and critical review; All authors were involved in preparation of the manuscript.

Declaration of Interest: The authors have no conflicts of interest to report

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Abstract

Rationale: The natural history of recovery from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) remains unknown. Since fibrosis with persistent physiological deficit is a previously-described feature of patients recovering from similar coronaviruses, treatment represents an early opportunity to modify the disease course, potentially preventing irreversible impairment.

Objectives: Determine the incidence of and describe the progression of persistent inflammatory interstitial lung disease (ILD) following SARS-CoV2 when treated with prednisolone.

Methods: A structured assessment protocol screened for sequelae of SARS-CoV2 pneumonitis. 837 patients were assessed by telephone four weeks after discharge. Those with ongoing symptoms had outpatient assessment at six weeks. Thirty patients diagnosed with persistent interstitial lung changes at multi-disciplinary team meeting were reviewed in the interstitial lung disease service and offered treatment. These patients had persistent, non-improving symptoms.

Results: At four weeks post-discharge, 39% of patients reported ongoing symptoms (325/837) and were assessed. Interstitial lung disease, predominantly organising pneumonia, with significant functional deficit was observed in 35/837 survivors (4.8%). Thirty of these patients received steroid treatment, resulting in a mean relative increase in transfer factor following treatment of 31.6% (standard deviation ± 27.6, $p < 0.001$), and FVC of 9.6% (standard deviation ± 13.0, $p = 0.014$), with significant symptomatic and radiological improvement.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Conclusion: Following SARS-CoV-2 pneumonitis, a cohort of patients are left with both radiological inflammatory lung disease and persistent physiological and functional deficit. Early treatment with corticosteroids was well tolerated and associated with rapid and significant improvement. This preliminary data should inform further study into the natural history and potential treatment for patients with persistent inflammatory ILD following SARS-CoV2 infection.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

In late 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, and has since spread globally, infecting over 31 million people. The clinical course of infection appears to be extremely variable, from asymptomatic to severe pneumonia with multi-organ failure requiring critical care. At time of writing, at least 1,122,036 people are known to have died following infection, but data on morbidity in survivors is scarce. Lung injury is a predominant feature of acute SARS-CoV2 infection, and understanding the longer-term implications is critical given the number of affected patients.

The most common radiological pattern of acute infection with SARS-CoV2 is of bilateral ground glass opacification with or without consolidation in a sub-pleural distribution, and a radiological and histological pattern of organising pneumonia pattern is described in many cases.[1-2] Radiological findings alter as the disease progresses, but persistent CT abnormalities beyond day 14 of symptoms and up to day 37 have been reported.[3,4]

However, no data exist as to the natural history of inflammatory infiltrates during recovery from SARS-CoV2 nor the utility of any treatment in patients with persistent inflammatory interstitial lung disease (ILD) following infection with coronavirus. However, corticosteroids are the mainstay of treatment for organising pneumonia of other causes,[5] and when used acutely in the management of acute respiratory distress syndrome (ARDS) caused by SARS-CoV2 have been associated with a reduction in mortality.[6,-7]

While interest in potential pulmonary, and specifically fibrotic, complications post SARS-CoV-2 infection grows, the long-term respiratory morbidity remains unclear.[8] Given the number of infected patients, persistent functional deficits in even a relatively small proportion is likely to represent a significant disease burden and prompt therapy may avoid potentially permanent

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

fibrosis and functional impairment. In this study, using a structured assessment protocol, we aimed to establish the incidence of persistent inflammatory ILD in patients post-infection with SARS-CoV-2, and to report the progression of disease when treated with steroids.

Methods

Study Design

This was a single-centre prospective observational study of patients with a diagnosis of SARS-CoV2 pneumonitis six weeks after discharge from hospital. Following screening anyone with ongoing symptoms underwent structured assessment and patients identified as having ILD at MDT and were further reviewed in the interstitial lung disease service. When clinically appropriate, they were offered treatment with corticosteroids following detailed discussion of the risks and benefits. For safety, patients were followed up weekly by telephone by an ILD specialist nurse and had access to a telephone helpline. At three weeks patients had repeat lung function and repeat high resolution CT and reviewed by a physician. This project was internally submitted for service improvement and accepted by the quality improvement and patient safety committee (REF 11007) prior to commencement, and external ethical approval was not required.

Identification of Patient Cohort

All patients presenting to Guy's and St Thomas' NHS Foundation Trust (a central London teaching hospital and tertiary ILD unit) with either a PCR diagnosis of SARS-Cov2 infection, or a

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

negative swab but a highly suspected clinical/radiological diagnosis were contacted by telephone four weeks after their discharge. They were asked if they had returned to their baseline. Patients with ongoing symptoms were invited to a structured clinical assessment and reviewed by a senior respiratory or infectious diseases physician. Patients whom declined review were excluded and any patients who reported that they had fully recovered were offered a chest radiograph at 12 weeks in line with UK national guidance.[9]

The final cohort included in the study were adults aged >18 who received an in-hospital diagnosis of SARS-CoV2 pneumonitis, who had persistent symptoms and an MDT-diagnosis of resultant ILD at 6-weeks post-discharge and consented to treatment with oral corticosteroids.

Structured Clinical Assessment

All patients attending clinic had a chest radiograph on arrival. They underwent measurement of vital signs and body mass index (BMI). Current Medical Research Council (MRC) Dyspnoea score was recorded, and they were asked to retrospectively report their function prior to their illness. Lung function, six-minute walk tests (6MWT), echocardiography and electrocardiogram were available to assessing clinicians as clinically indicated on a per-patient basis. Blood tests were taken for renal profile, liver function, C-reactive protein, fibrinogen, D-dimer and ferritin. Following medical review, patients with ongoing physiological impairment as defined by desaturation of ≥ 4% or abnormal lung function, and/ or abnormal chest radiograph had chest computed tomography (CT) imaging on the day. Blood tests were taken for renal profile, liver function, C-reactive protein, fibrinogen, D-dimer and ferritin. Relevant radiological results were discussed in a specially-convened weekly post-COVID MDT comprising 3 specialist chest

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

radiologists and 15 respiratory and infectious diseases specialists. This allowed for institutional learning and refinement of our understanding of the condition and its imaging.

Treatment

Patients who were identified as having post-SARS-Cov2 ILD at the post-COVID MDT were invited to attend the interstitial lung disease service for consideration of treatment with corticosteroids. These patients were recovered from their initial infection and were assumed to have cleared the virus based on their biochemical markers and known timeframe for clearance.[10] Every patient had a detailed discussion regarding their proposed treatment and understood the rationale and potential side effects.

Patients were only offered treatment in the absence of reported weekly improvement in symptoms and in the presence of a combination of MDT-confirmed ILD with physiological and functional impairment as demonstrated by 6MWT, and lung function with gas transfer

Statistical Analysis

Values are expressed as mean ± standard deviation (SD) or median ± interquartile range (IQR). Change in FVC and TLCO, MRC, 6MWT distance and SpO2 and biomarkers were analysed using paired samples t-test. Adverse events and radiology are reported descriptively. Analysis was performed using SPSS version 26 (IBM) and GraphPad Prism version 8 (GraphPad Software, La Jolla, California USA).

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Results

Between 28th-February and 29th May 2020, 1272 patients were diagnosed with SARS-CoV2 pneumonitis in our hospital, either following an accident and emergency attendance, or hospital admission (figure 1). Of these, 1239 had a positive PCR result, and the remainder had a clinic-radiological diagnosis made during their hospital attendance given the sensitivity of CT in diagnosing SARS-CoV2 pneumonitis.18 Mortality was 19.1% (245 patients). At the time of writing, 74 patients (6%) remained an inpatient. Of the remaining patients 88% were included in the study (837/953). One hundred and sixteen patients (9%) did not respond to two phone calls and a letter. Electronic health record data confirms that 4 of the 116 patients whom we were not able to contact at 28 days had died.

All remaining 837 patients were initially screened by telephone. Of these, 316 (38%) reported having fully recovered. Ongoing symptoms were reported by 325 patients (39%) and these were offered structured assessment. Following acceptance of initial invitation, a further 57 patients screened by telephone (9%) declined any follow up and 139 (16%) were unable to attend the hospital but were included in the analysis.

Outcomes Following Structured Outpatient Clinical Assessment

Of the 325 patients who had ongoing symptoms at telephone screening and attended structured assessment, 138 (42.9%) had no evidence of physiological impairment or persistent change on chest radiograph and were discharged with reassurance or offered formal rehabilitation. Functional or physiological impairment was observed in 110 (33.8%) in the

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

absence of any radiological evidence of persistent lung disease or pulmonary embolism. These patients were appropriately referred to cardiology, nephrology, diabetes, psychology or rehabilitation services via pre-agreed pathways. Following CT imaging, 77 patients (24%) were referred to the post-COVID lung disease MDT by their clinician.

Radiological Findings

At MDT, of the 77 patients referred, 59 (76.6%) of those imaged at six weeks were found to have persistent parenchymal abnormality presumed to be related to their previous infection. Diagnosis was made based on the MDT consensus of the radiological pattern, and lung biopsy was not performed. A spectrum of findings was observed including patients who had near complete resolution of chest radiographic changes but with abnormal CT. Others had persistent changes on both chest radiograph and CT. In the majority, the pattern observed on initial follow up CT represented an organising pneumonia-like pattern. Findings of bilateral sub-pleural ground glass infiltrates with a mid to lower zone distribution were described as organising pneumonia.

In a proportion of cases, this was also associated with sub-pleural and peribronchial linear dense consolidation. Some patients presented at first follow-up imaging with varying degrees of traction bronchiectasis which may reflect parenchymal fibrosis, consistent with a fibrotic organising pneumonia pattern.

Of the 18 patients who did not have COVID-related imaging changes, 3 had normal lung parenchyma. The remainder had new findings of pulmonary embolus (1 patient), lung infarct (1 patient) klebsiella pneumonia (1 patient), pneumocystis jirovecii pneumonia, (1 patient), and

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

lung nodule (1 patient). Some pre-existing disease was identified which included connective-tissue disease –associated ILD (CTD-ILD, 1 patient), bronchiectasis (2 patients), sickle lung disease (1 patient) and airways disease (1 patient).

ILD MDT Outcomes

Of the 59 patients with persistent post-COVID interstitial change, the majority (59%) had organising pneumonia. In three patients (5.0%) who had previously received steroid treatment, the pattern was felt to be fixed, with only minor ground glass (<15% of lung involvement). A further 21 patients (38.9%) had limited disease with pure ground glass with <15% lung involvement and a scattered distribution or had no functional impairment. In the remaining 35 patients (66%) given the presence of organising pneumonia with restrictive physiology and in the absence of improving symptoms treatment with corticosteroids was recommended. The remaining patients were followed up at three months with CT and lung function. In 5 patients (22%) where therapy was recommended it was decided by mutual agreement with the patient and clinician that steroid treatment was not appropriate, either due to comorbid disease or limited/improving symptoms, meaning that 30 patients completed treatment and follow up.

Patients were treated at day 61 (± 19) post-discharge. A maximum initial dose of 0.5mg/kg prednisolone was proposed based on the local standard protocol for managing organising pneumonia The average starting dose was 26.6mg and a rapid wean over three weeks was felt to be appropriate given the presumed lack of an ongoing driver of inflammation. In some cases, the dose was reduced by the treating clinician in view of comorbid disease. (Figure 2).

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Characteristics of Patients with Persistent Inflammatory Interstitial Lung Disease

Patients with post-COVID ILD were predominantly male (71.5%) and overweight with a mean BMI of 28.3 ± 4.0, although only 26% were obese (Table 1). Most had at least one co-morbidity, with the commonest being diabetes and asthma (22.9%). The mean admission was 16.9 ± 12.5 days. Oxygen therapy was required by 82.9%, with half (55%) requiring intensive care unit (ICU) admission and 46% requiring invasive mechanical ventilation (Table 2).

Biochemical markers indicated improving systemic inflammation on follow up, with CRP falling from a mean of 230.2 ± 162.6mg/L at peak illness, to 30.9 ± 37.5mg/L at discharge and 6.1 ± 9.79mg/L in clinic. Likewise, ferritin was high at the peak with a mean of 1592.4 ± 1274.6ug/L, falling to 807.6 ± 450.0ug/L at discharge and 179.0 ± 141.8ug/L on structured assessment. Patients had a high d-dimer during their admission 17.2± 8.1mg/L, and whilst this had fallen by six weeks, it was persistently elevated at 2.35 ± 3.7mg/L (Table 3).

Following structured assessment, we demonstrated that patients with persistent ILD had both functional and physiological impairment. Patients reported their MRC at their 6-week structured assessment as 3 (±2) and reported their pre-COVID MRC as 1(±2). Pulmonary function testing at follow up demonstrated a mean FVC of 91.9% predicted (± 15.9), and TLCO 60.6% predicted (± 24.9) (Table 4). These were slightly lower in the treated cohort with a mean FVC of FVC 86.4% (± 16.3), and TLCO 56% (± 19.6).

Response to Therapy

Thirty patients completed treatment and follow up with clinical review, CT scan and pulmonary function tests. All 30 patients report that their breathlessness and function had significantly

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

improved following treatment with prednisolone, and median MRC had improved from 3 (± 2) to 2 (± 1) (p=0.002). This was associated with a mean relative increase in FVC of 9.6 % (±13.6) at three weeks, and the mean increase in TLCO was 31.49% (± 27.7), which reached statistical significance (Table 5). One patient could not perform lung function, and 6MWT was used to assess response instead. At structured assessment they were able to walk 130m (33.0% predicted) and desaturated to 89%. Following treatment, they completed 343m (86.6% predicted), and minimum SpO2 was 92%. No major complications of steroid treatment were observed.

All post-steroid CT imaging was re-discussed at MDT. In all cases, the consensus was that the CT features had improved. Repeat imaging demonstrated resolution of the more solid components, leaving a subtler ground glass pattern in the same distribution. Where the pattern was initially pure ground glass, the density of these changes decreased uniformly post-treatment. At three weeks follow up imaging, we did not observe the progression of inflammatory change to any fibrosis. A typical response is demonstrated in Figure 4, and with further examples in supplementary figures 2 and 3. However, the significance of any residual changes remains unknown and will require further longitudinal imaging.

Follow up has been performed for three patients who following discussion and patient choice, did not receive steroids. Imaging was performed in two cases and revealed a degree of improvement in the ground glass component, although of note, both follow up scans also demonstrated traction bronchiectasis. Mean increase in FVC at three months was 8.9% and mean increase in TLCO was 6.9%.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Discussion

Here we describe the characteristics of a large cohort of patients recovering following hospital admission with COVID-19, including those who had residual pulmonary disease at 6-weeks post-discharge. Thirty patients had persistent interstitial changes suggestive of organising pneumonia and were treated with oral prednisolone. The objective was to prevent the development of pulmonary fibrosis with permanent functional deficit which has been observed in the long term follow up of SARS-CoV1.[11,12]

Our telephone screening identified a cohort of persistently symptomatic patients and allowed rapid clinical triaging. Following formal assessment, a cohort of patients were identified who had both radiological inflammatory lung disease (of organising pneumonia-type) and persistent physiological and functional deficit at six weeks. The natural history of the disease at this time point has not previously been described, and the lack of a known recovery trajectory is a limitation of this study. It is difficult to tease out from a single time point what imaging changes are simply part of the normal recovery from lung injury. It seems likely that the patients with <15% involvement, especially given their relatively preserved lung function, may represent the 'typical' recovery trajectory. However, following lung injury/ ARDS due to other causes the predominant radiological pattern is not typically that of organizing pneumonia. [19,20] Indeed, drawing parallels from other coronavirus infections, it is likely that in the absence of intervention, some patients might have been left with persistent functional deficits and permanent fibrotic change. ILD was diagnosed in 4.8% of patients who survived their original infection and 10.8% of the total patients with persistent symptoms and included those patients

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

with relatively mild disease who did not require more than 24 hours of oxygen therapy. This may be an underestimate of the true prevalence given the proactive use of corticosteroids in ICU at our site during the first wave in the United Kingdom. However, given the now-established benefit of dexamethasone in hospitalised patients, this study will reflect clinical practice worldwide in subsequent waves..[6,7]

Radiologically the interstitial abnormalities detected post COVID-19 were dominated by an organising pneumonia phenotype (59%). The confidence of the MDT diagnosis meant that neither bronchoalveolar lavage (BAL) nor lung biopsy was undertaken on this cohort, but clearly this is an area for future research. A number of subjects had minimal residual disease and no physiological impairment (25%) and reassuringly there was not a predominance of established fibrotic lung disease, despite the numbers of patients requiring ICU and invasive mechanical ventilation (46%). As anticipated in screening such a population with significant co-morbidities previously undiagnosed respiratory conditions were also diagnosed including IPF and CTD-ILD. The radiological pattern of organising pneumonia is concordant with the known post-mortem findings of COVID-19[3,15] though we demonstrate its persistence in convalescent patients. Steroids are the accepted first-line treatment of organising pneumonia of other causes, and it was with this rationale that post COVID-19 patients were treated. In patients with >15% lung involvement on CT scan and impairment of their respiratory function we demonstrate a good response to immunosuppressive therapy. The treatment was well tolerated, and there was a dramatic increase in spirometry and gas transfer at three weeks with functional improvement in a group of patients whose clinical trajectory had plateaued prior to treatment. The clinical improvement was mirrored in the imaging, with radiological resolution of the inflammatory

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

changes. This was not primarily a radiological study and the CT scans were not formally scored pre/post treatment. However, each case was discussed before and after treatment at MDT with three senior radiologists semi-quantitatively in line with standard ILD MDT practice and the findings paired with the improvement in patient reported function and physiological parameters. In addition to this there are several other limitations to our work. Firstly, there is some difficulty is understanding whether imaging and clinical findings represented nothing other than slow ongoing recovery. This was not a randomised control trial and treatment regimens were drawn from established best-practice protocols to treat organising pneumonia triggered by other factors. While we have seen good resolution following initial therapy, patients with interstitial changes will require close follow up to observe and to understand the evolution of this condition. However, drawing parallels with organising pneumonia secondary to other triggers it is unlikely once resolved this will reoccur.

The small number of patients who remain inpatient may mean we have underestimated the true prevalence the inflammatory disease. However, even at these estimates given the continually escalating number of cases worldwide there is likely to be a large cohort of patients at risk for these inflammatory sequelae and would clearly benefit from early assessment and prompt therapy to prevent long-term irreversible lung damage. These preliminary data should inform further study into both the natural history and potential treatment for patients with a persistent inflammatory interstitial lung disease following SARS-CoV-2 infection.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

References

1 Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation between chest CT findings and clinical conditions of coronavirus disease (covid-19) pneumonia: A multicenter study. *Am J Roentgenol* 2020; **214**: 1072–7.

2 Bradley BT, Maioli H, Johnston R, *et al.* Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020; **396**: 320–32.

3 Pan F, Ye T, Sun P, *et al.* Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology* 2020; **295**: 715–21.

4 Wang Y, Dong C, Hu Y, *et al.* Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. *Radiology* 2020; **296**: E55–64.

5 Cordier JF. Organising pneumonia. *Thorax* 2000; **55**: 318–28.

6 Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Engl J Med* 2020; : 1–11.

7 Sterne JAC, Murthy S, Diaz J V., *et al.* Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. *JAMA - J Am Med Assoc* 2020; **324**: 1330–41.

8 George PM, Barratt SL, Condliffe R, *et al.* Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax* 2020; **75**: 1009–16.

9 BTS guideline. file:///C:/Users/Kate/AppData/Local/Packages/Microsoft.MicrosoftEdge_8wekyb3d8bbwe/TempState/Downloads/Resp follow up guidance post covid pneumonia (1).pdf.

10 He X, Lau EHY, Wu P, *et al.* Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26**: 672–5.

11 Hui DS, Joynt GM, Wong KT, *et al.* Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; **60**: 401–9.

12 Zhang P, Li J, Liu H, *et al.* Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Res* 2020; **8**. DOI:10.1038/s41413-020-0084-5.

13 Matthay MA. Acute respiratory distress syndrome. *Acute Respir Distress Syndr* 2003; **2**: 1–566.

14 Wilcox ME, Patsios D, Murphy G, *et al.* Radiologic outcomes at 5 years after severe ARDS. *Chest* 2013; **143**: 920–6.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Figure Legends:

Figure 1. Flowchart of the study population recruited between February and May 2020. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; CT: computed tomography; MDT: Multidisciplinary meeting.

Figure 2. Steroid dosing by week. Data are presented as median and interquartile range.

Figure 3. Change in lung function following treatment with oral prednisolone in patients with interstitial lung disease following infection with SARS-CoV-2.

Figure 4. Axial image and coronal reconstruction from CT thorax acquired immediately prior to discharge in a previously fit and well 57-year-old man [Image 4a, 4b] shows radiological pattern of OP disease with predominant peribronchial and perilobular dense consolidation mild traction bronchiectasis of the airways. At this stage the patient could only walk 30 yards. Follow-up CT thorax acquired after three weeks of oral prednisolone [Image 4c, 4d] shows resolution of consolidation with residual ground glass and fine subpleural reticulation. The airways still have a slightly non-tapering appearance. The patient was now able to run for 30 minutes a day.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Table 1: Baseline characteristics of patients with interstitial lung disease following infection with SARS-CoV-2. Data are presented as percentage value or mean ± standard deviation (SD) as appropriate. CKD: Chronic Kidney Disease; HIV: Human Immunodeficiency Virus; COPD: Chronic Obstructive Pulmonary Disease.

n=35		
Age		60.5 ± 10.7
Sex	**Male**	25 (71.4%)
	Female	10 (28.6%)
BMI		28.3 ± 4.0
Smoking history	**Ever smoker**	21 (34.2%)
	Never smoker	14 (65.7%)
Comorbidities	**Obesity**	9 (25.7%)
	Hypertension	11 (31.4%)
	Diabetes	8 (22.9%)
	CKD	2 (5.8%)
	HIV	1 (2.9%)
	Sickle cell	1 (2.9%)
	Asthma	8 (22.9%)
	COPD	2 (5.8%)
	Pre-existing ILD	0

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Table 2: Admission data from patients with interstitial lung disease following infection with SARS-CoV-2. Data are presented as percentage value or mean ± standard deviation (SD) unless otherwise stated.

Admission data	
Length of Stay ~~LOS~~ (Mean ± SD)	16.9 ± 12.5
O2 therapy (>24 hours)	29 (82.9%)
Max O2 requirement (%) (Median ± IQR)	38.0 ± 48
Days O2 therapy (Median ± IQR)	13.9 ± 12.1
Steroid treatment (Inpatient)	6 (17.1%)
Critical care admission	19 (54.5%)
Invasive mechanical ventilation	16 (45.7%)
SpO2 on discharge	95.1 ± 2

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Table 3: Patients demonstrated improvement in markers of systemic inflammation at six weeks post-discharge. Normal values are presented in brackets for each marker. Data are presented as percentage value or mean ± standard deviation (SD) unless otherwise stated. CRP: C-Reactive Protein

	Peak	**Discharge**	**Clinic**
CRP (0-4mg/L)	230.2 ± 162.6	30.9 ± 37.5	6.1 ± 9.79
Ferritin (30-400ug/L)	1592.4 ± 1274.6	807.6 ± 450.0	179.0 ± 141.8
Fibrinogen (1.7-3.9g/L)	12.3 ± 1.1	5.4 ± 1.6	4.2 ± 2.6
D-dimer (0.00-0.55mg/L)	17.2± 8.1	10.2 ± 6.7	2.35 ± 3.7
Creatinine (59-104umol/L)	150.2 ± 30.3	87.6 ± 89.0	62.5 ± 33.2
	Nadir	**Discharge**	**Clinic**
Lymphocyte (1.2-3.5 x10^9)	0.7± 0.2	1.6 ± 0.5	2.7 ± 1.4

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Table 4: Results following structured assessment of patients with interstitial lung disease following infection with SARS-CoV2. Data are presented as percentage value or mean ± standard deviation (SD) unless otherwise stated. MRC: Medical Research Council; FEV1: Forced Expiratory Volume in 1s; FVC: Forced Vital Capacity; TLCO: Transfer Factor of the lung for Carbon Monoxide; KCO: Transfer Coefficient

Structured assessment		
Resting SpO2 (%)		95.5 ± 3
MRC Dyspnoea Score (Median ± IQR)	**Pre-COVID**	1.0 (0-3)
	Post-COVID	3.00 (1-5)
6MWT distance (m)		291.2 ± 153.2
6MWT (% predicted)		54.9 ± 25.0
6MWT min SpO2		90.0 ± 6
Lung function	**FEV1 (L)**	2.4 ± 0.7
	FEV1 (%)	86.0 ± 13.7
	FVC (L)	3.2 ± 1.0
	FVC (%)	91.9 ± 16.0
	FEV1/FVC (%) (Median ± IQR)	77.8 (73.2-82.4)
	TLCO (SI)	5.6 ±2.2
	TLCO (%)	60.6 ±24.9
	KCO (TLCO/L)	1.3± 0.3
	KCO (%)	88.0 ± (87.6 – 88.15)

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

Table 5: Follow up data from patients with interstitial lung disease following infection with SARS-CoV-2. Data are presented as percentage value or mean ± standard deviation (SD) unless otherwise stated. FEV1: Forced Expiratory Volume in 1s; FVC: Forced Vital Capacity; TLCO: Transfer Factor of the lung for Carbon Monoxide; KCO: Transferr Coefficient

n = 30	**Pre-treatment**	**Post-treatment**	**Mean difference (95% CI)**	**p**
FVC (L)	3.07 ± 1.12	3.36 ± 1.11	0.42 (0.28 – 0.56)	0.014
FVC (%)	86.8 ± 18.5	99.2 ± 19.1	9.63 (4.49 –14.7)	0.004
TLCO (SI)	5.56 ± 2.56	7.05 ± 2.42	1.72 (1.18 – 2.25	<0.001
TLCO (%)	59.7 ± 21.1	82.6 ± 15.7	22.3 (14.1-32.5)	<0.001
KCO (TLCO/L)	1.25 ± 0.34	1.83 ± 0.36	0.27 (0.16-0.37)	0.025
KCO (%)	82.9± 28.8	104.3 ± 24.0	19.9 (9.72-30.1)	0.002

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

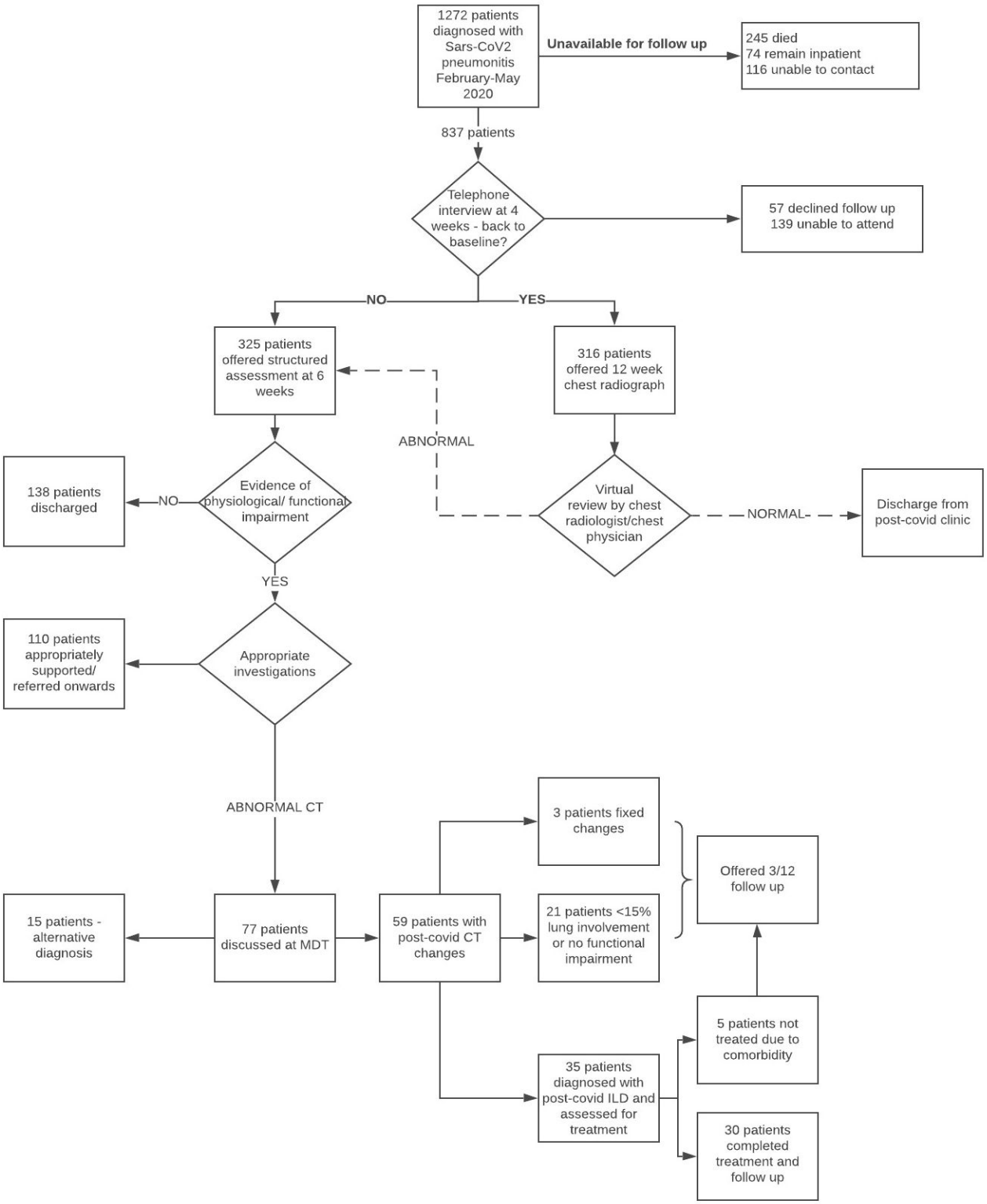

Figure 1: Flowchart of the study population recruited between February and May 2020. SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; CT: computed tomography; MDT: Multidisciplinary meeting

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

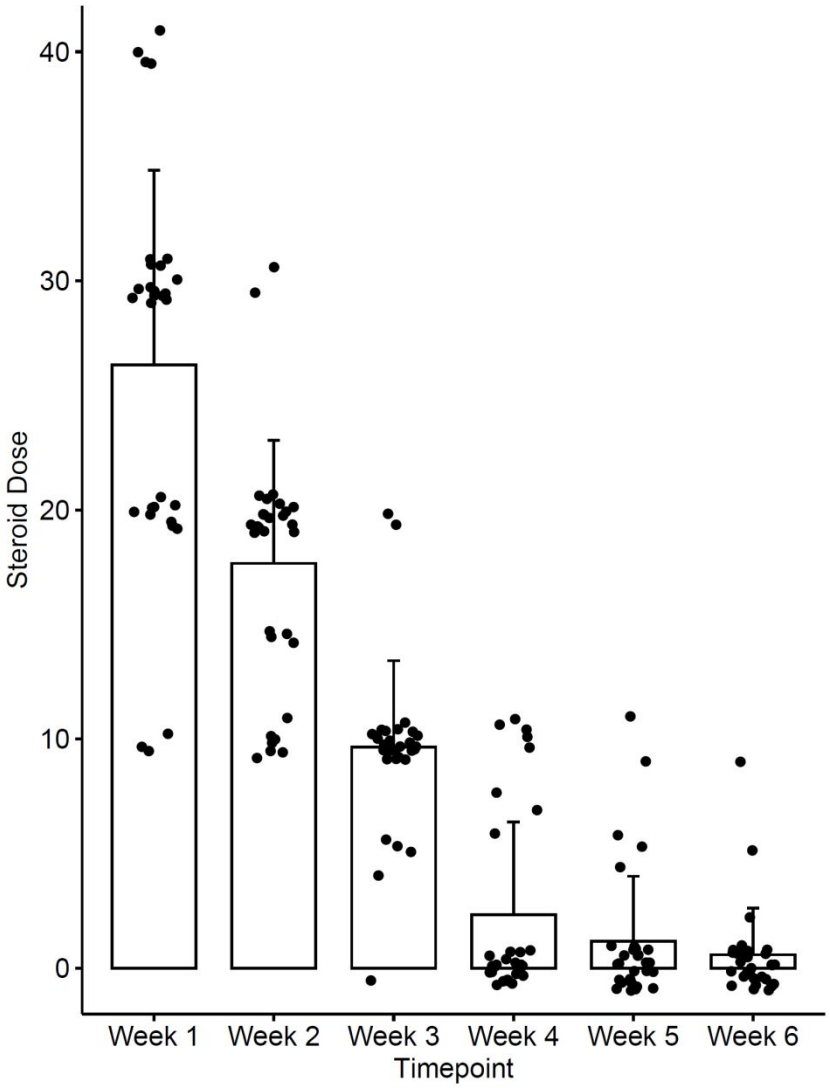

Figure 2: Steroid dosing by week. Data are presented as median and interquartile range.

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

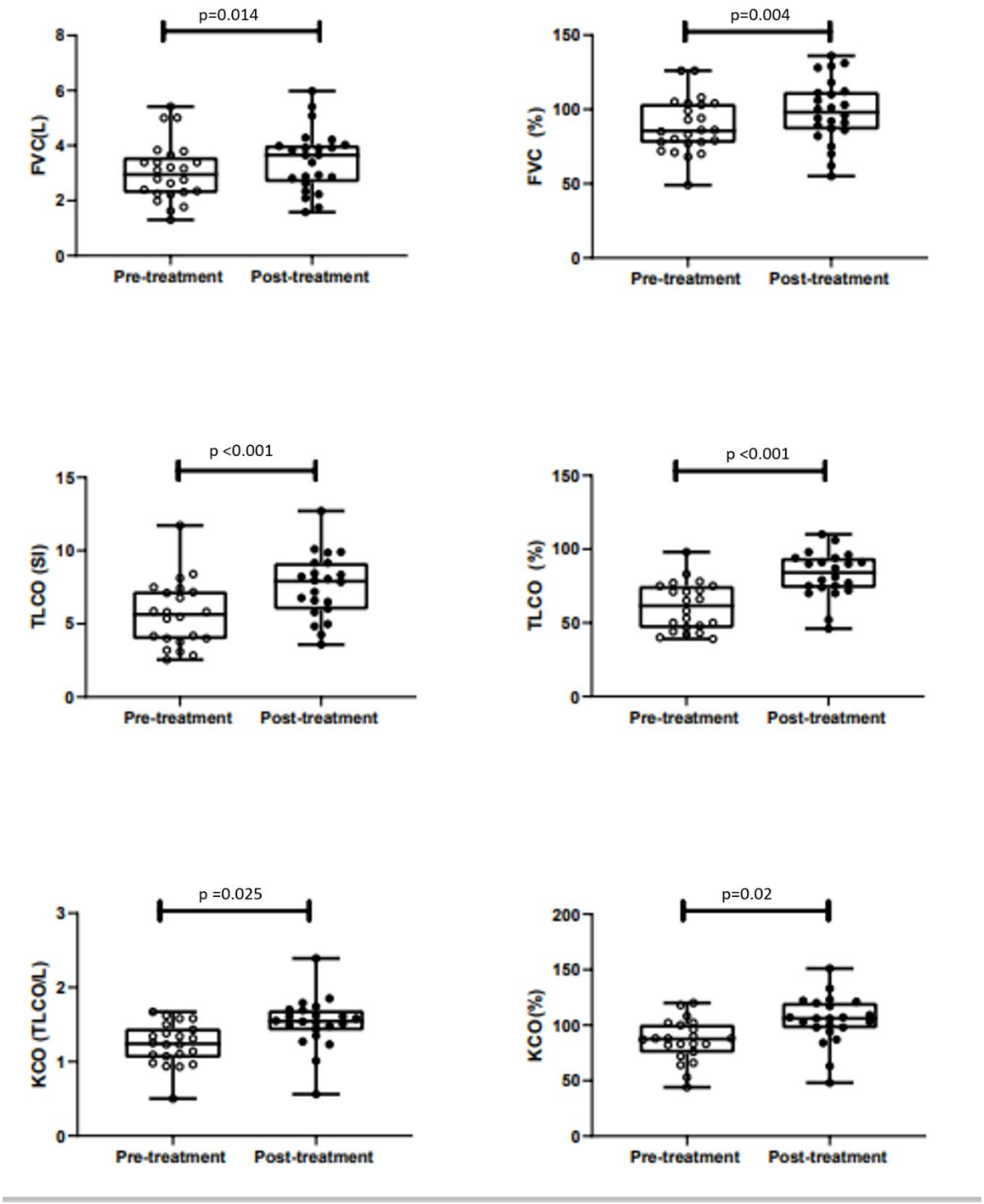

Figure 3: Change in lung function following treatment with oral prednisolone in patients with interstitial lung disease following infection with SARS-CoV-2

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC

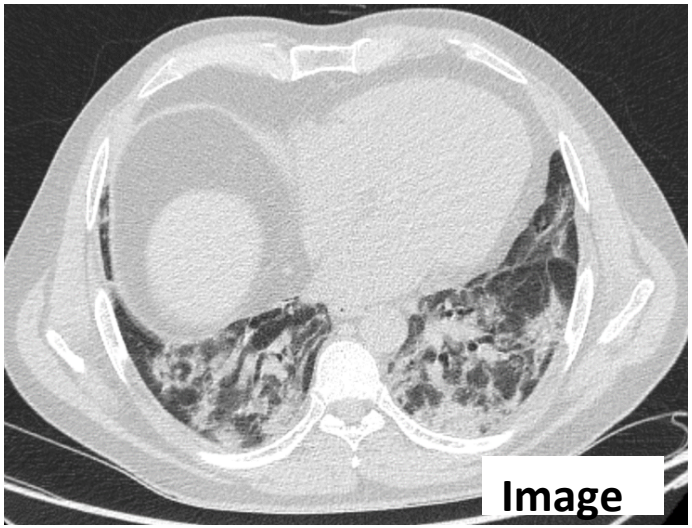

Image 4.a

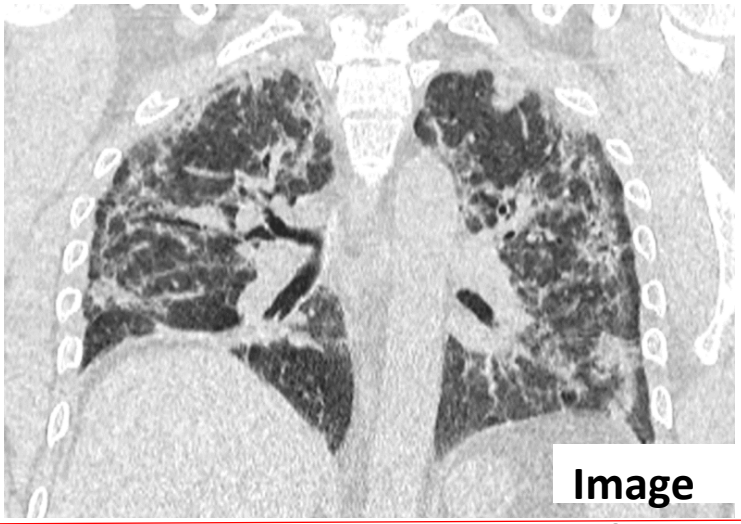

Image 4.b

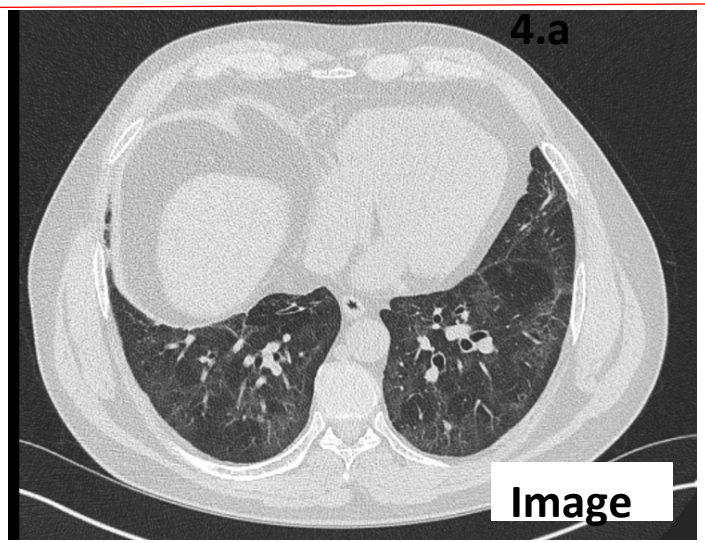

Image 4.c

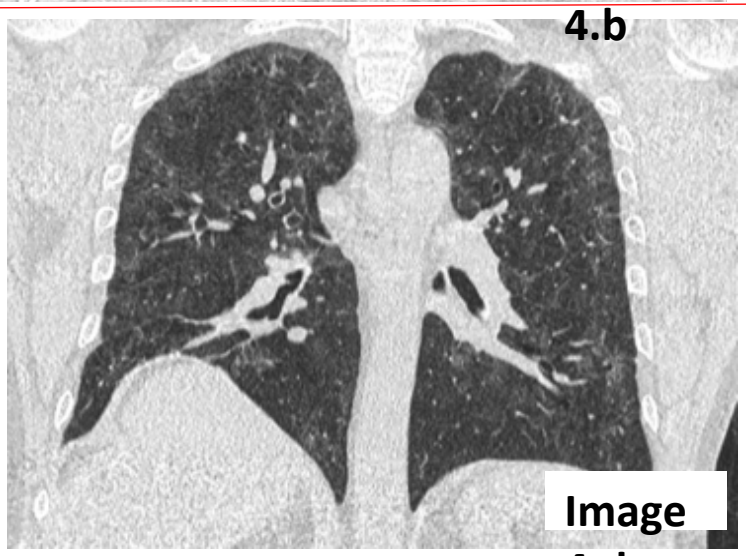

Image 4.d

ANNALSATS Articles in Press. Published January 12, 2021 as 10.1513/AnnalsATS.202008-1002OC