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## TITLE

COVID-19 IN LUNG TRANSPLANT RECIPIENTS: A CASE SERIES FROM MILAN, ITALY.

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## ABBREVIATIONS

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BAL - Bronchoalveolar lavage  
bpm – breaths per minute  
CARV – community acquired respiratory viruses  
COVID-19 - Coronavirus Disease 2019  
CLAD - Chronic Lung Allograft Dysfunction  
CPAP – Continuous Positive Airway Pressure  
CPFE – Combined Pulmonary Fibrosis and Emphysema  
CT – Computed Tomography  
CXR – Chest X Rays  
DSA – Donor Specific Antibodies  
ER – Emergency Room  
FEV1 – Forced expiratory volume at 1 second  
GFR – Glomerular Filtration Rate  
GGO – Ground Glass Opacities  
ICU – Intensive Care Unit  
IST – Immunosuppressive Therapy  
IVIG – Intra Venous Immunoglobulin  
LMWH – Low Molecular Weight Heparin  
LPM – Liters Per Minute  
LuTx – Lung Transplantation  
NC – Nasal cannula  
NEJM – New England Journal of Medicine  
NSIP – Non Specific Interstitial Pneumonia  
OSA – Obstructive Sleep Apnea  
PEEP – Positive End Expiratory Pressure  
P/F –  $\text{PaO}_2/\text{FiO}_2$  ratio  
RA – Room Air  
RR – Respiratory Rate  
TPE – Therapeutic Plasma Exchange  
VM – VenturiMask  
WHO – World Health Organization

## ABSTRACT

Limited data is currently available regarding the course of COVID-19 in lung and solid organ transplant recipients.

We hereby present 4 cases of SARS-CoV-2 pneumonia in lung transplant recipients from our centre, set in Milan, Italy. We reduced immunosuppressive regimen in all these patients, typically holding the antiproliferative agent and augmenting steroids; everybody received hydroxychloroquine, initial empiric antibiotic treatment with piperacillin/tazobactam and high dose low molecular weight heparin. Clinical course seemed favourable in three of our patients, but one of them deteriorated after 10 days of hospitalization, probably due to an acute form of graft dysfunction triggered both by COVID19 and a nosocomial bacterial infection, and eventually died.

Although short-term prognosis could be considered benign in the majority of our patients, we should carefully monitor these individuals in order to detect early sign of clinical deterioration and graft dysfunction in the next few months.

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19), being declared a public health emergency in Italy since January 30<sup>th</sup> and a pandemic by WHO since March 11<sup>th</sup>, is an emerging infection and has caused 162.488 confirmed cases and 21.067 deaths in Italy only, as of April 14<sup>th</sup>, 2020. The hardest hit region in Italy is Lombardy, where our transplant centre is set.

Early guidelines [1] were released in order to optimise management of lung transplantation (LuTx) candidates and recipients, with reference to organ donation and recovery, candidates selection and recipients follow up. However, there is currently a paucity of data on the course of the disease in lung and solid organ transplant recipients.

We hereby report the first four SARS-CoV-2 pneumonia in LuTx recipients at our institution.



## CASE SERIES

Table 1 reports baseline characteristics of our patients, while Table 2 summarises gas exchange and blood tests results.

### Case 1

The first case we report is that of a 48-year-old male, who received bilateral LuTx for cystic fibrosis in April 2014.

On March 13<sup>th</sup>, he was admitted to our ER for fever, malaise and worsening dyspnea on exertion, which started 72 hours before. His swab turned positive for SARS-CoV-2; his blood tests showed lymphocytopenia, worsening kidney function and mild increase of c-reactive protein, his chest X-rays (CXR) scan revealed bilateral peribronchial thickening.

Initial treatment included hydroxychloroquine, piperacillin/tazobactam and levofloxacin, and CPAP during the night for support. We decided to temporarily hold everolimus and anticoagulation was switched from warfarin to low molecular weight heparin (LMWH).

Because of persistent fever, a chest CT scan was obtained, showing bilateral patchy ground glass opacities (GGO), see Figure 1; blood cultures were negative.

Clinical stability was reached after 7 days from admission, with apyrexia and normalisation of biomarkers of inflammation. He was discharged on day 12, with good gas exchange on room air (RA) (P/F 390 on March 25<sup>th</sup>).

On April 8<sup>th</sup> and 9<sup>th</sup>, two consecutive specimens of nasopharyngeal swabs were obtained and both turned negative for SARS-CoV-2. His FEV1 was 96% of baseline on May 4<sup>th</sup> (outpatient evaluation).

### Case 2

On March 21<sup>st</sup>, a 57-year-old lung transplanted female was admitted to our ER because of malaise and mild dyspnoea on exertion; her swab was positive for SARS-CoV-2.

P/F on admission was almost normal (390 on RA, pO<sub>2</sub> 78, hypocapnia, respiratory rate (RR) 28 bpm) and her CXR revealed an infiltrate in right lower lobe; CT scan was then obtained (Figure 2A), showing bilateral lung involvement. Lymphocytopenia was the only significantly altered blood test, inflammation biomarkers were almost normal. High flow rate of supplemental oxygen therapy with VenturiMask (VM) 40% 8 LPM was promptly initiated, improving both oxygen saturation and RR. We decided to withhold azathioprine

and started hydroxychloroquine, piperacillin/tazobactam and IV metilprednisolone 20 mg b.i.d.; warfarin was switched to LMWH.

Despite an initial benign presentation, hypoxemia continued slowly worsening. On March 27<sup>th</sup>, given a severely worsening P/F (180 in VM40%), we introduced CPAP support, with slow but progressive improvement. On April 7<sup>th</sup>, P/F was almost 300 in oxygen therapy with VM28%, CXR was better and inflammation biomarkers were decreased. However, 48 hours after, severe clinical deterioration occurred: she became CPAP dependent and acute interstitial syndrome was shown performing bedside lung ultrasound; no fever, no significant worsening of inflammatory biomarkers. After obtaining a new CT scan (progression of interstitial involvement, see Figure 2B), she underwent a bronchoscopy, revealing an endo-bronchial white plaque seen at the lower left lobe site, highly suspicious for fungal infection, and a large amount of secretions and mucous plugs. Apart from SARS-CoV-2, a strain of ESBL+ *K.pneumoniae* and *Aspergillus fumigatus* were also isolated on her BAL culture and we consequently introduced voriconazole and meropenem. Moreover, given the strong suspicion of progressing COVID-19, we also started the compassionate use of both anakinra and remdesivir.

However, her general clinical conditions worsened, with evidence for progressive ARDS and MOF; our transplant multidisciplinary panel made the difficult decision not to offer ICU support due to age, comorbidities, complications and poor prognosis. She eventually passed away on April 23<sup>rd</sup>.

### Case 3

Our third patient is a case of suspected hospital acquired COVID-19.

A 70-year-old man, who received single left LuTx in October 2014 for Combined Pulmonary Fibrosis and Emphysema (CPFE), was admitted to our ER for pulmonary exacerbation on March 17<sup>th</sup>; his first swab for SARS-CoV-2 was negative (double testing) and he was therefore hospitalised in a COVID-free ward, receiving piperacillin/tazobactam and doxycycline as first line therapy; CPAP support was also introduced. CT scan is shown in Figure 3A, raising the suspicion of fungal infection on right native lung; *Aspergillus* was then isolated on his sputum culture, prompting the decision to start voriconazole on his 6<sup>th</sup> day of hospitalization.

However, on April 1<sup>st</sup>, his (fifth) surveillance swab for SARS-CoV-2 turned positive; a new infiltrate was found in upper right lobe; no fever, no significant clinical and/or gas exchange deterioration, only slightly altered inflammatory biomarkers but no lymphocytopenia. Hydroxychloroquine was therefore initiated, together with antithrombotic prophylaxis with LWMH 70 UI/Kg b.i.d.

He was doing fine till April 10<sup>th</sup>, P/F 429 on oxygen therapy 2 LPM; he was waiting to be transferred to a COVID-19-dedicated rehabilitation centre. However, on April 11<sup>th</sup>, fever occurred (single peak, TA°C 38.5), with transient worsening of gas exchange (VM 40%); a new CT scan showed improvement of his native lung but new patchy GGO on left transplanted lung (see Figure 3B). A BAL was then obtained, but no other pathogen aside from SARS-CoV-2 was found, and antibiotic therapy was potentiated with IV meropenem.

He rapidly improved again and was finally discharged on April 24<sup>th</sup>, with acceptable gas exchange on RA (P/F 311).

#### **Case 4**

Our last case for this series is a 69-year-old lady, with a history of excellent graft function. She was admitted to our ER on April 6<sup>th</sup> with a 7 days history of hyporexia and nausea, severe malaise and low-grade fever, cough and worsening dyspnoea. Gas exchange on room air was almost normal, pO<sub>2</sub> 76 mmHg, hypocapnia, RR 18 bpm; chest CT scan revealed typical patchy bilateral GGO (see Figure 4); laboratory tests were consistent with typical COVID-19 presentation, revealing lymphocytopenia and mild alteration of c-reactive protein; a positive swab for SARS-CoV-2 confirmed the diagnosis. CPAP support was introduced as well as hydroxychloroquine and piperacillin/tazobactam; azathioprine was temporarily discontinued; she also received antithrombotic prophylaxis with LMWH 70 UI/Kg.

Clinical course was then uneventful; she was discharged on day 15, with good gas exchange on room air (P/F 386). On May 7<sup>th</sup> and 8<sup>th</sup>, two consecutive specimens of nasopharyngeal swabs were negative for SARS-CoV-2.

## DISCUSSION

Management of COVID-19 is still a matter of debate both in immunocompetent and immunosuppressed patients. Solid organ transplant recipients should be naturally considered more prone to develop SARS-CoV-2 pneumonia as for any other CARV.

However, unlike common viruses [2; 3], Coronaviruses have not shown an increased severity and/or mortality in immunosuppressed patients. The main driver of lung tissue damage in the course of this kind infection seems to be the host innate immune response.

Aslam and colleagues recently suggested that immunosuppressive therapy with calcineurin inhibitor (Tacrolimus or FK506 and Cyclosporin A) may diminish the clinical expression of disease thanks to its anti-inflammatory effects [4]. Indeed, Tacrolimus exerts its immunosuppressive effects mainly through impairment of gene expression in target cells, particularly that of interleukin-2, which is a crucial regulator of proliferation, survival and maturation for T cells [5]. Together with mycophenolate, Tacrolimus reduces also interleukin 17, consequently inhibiting Th17-related immune response [6]. However the very limited existing evidence regarding mycophenolate in coronavirus infections suggests that it is likely to cause more harm than benefit for SARS-CoV-2 pneumonia, supporting its discontinuation [7]. Two laboratory studies involving cell line cultures investigating potential antiviral therapeutic targets found that FK506 inhibited viral replication of SARS-CoV, HCoV-NL63 and HCoV-229E [8]; however tacrolimus has never been tested in humans for this purpose and the novel COVID19 may have different pathogenic mechanisms than those of the above mentioned viruses [9].

It has already been postulated that lymphocytopenia could be caused by lung sequestration of hyper-activated T cell and immunosuppressive drugs could thus limit this effect [10]. Three of our patients presented with lymphocytopenia, which was absent at their previous routine examinations.

So far, clinical presentation at admission and clinical course seemed quite similar to those described for non-transplanted individuals, with a not worse short-term outcome than general hospitalised individuals in the majority of our patients. However we suffered the death of one of our patients, despite optimization of treatment. This finding may be similar to what has already been reported in other centres and, more in general, in solid organ transplant recipients, with mortality rates up to 20-25% [11-13]

Apart from immunosuppression, each of our patients presented at least one risk factor for mortality in COVID-19 (diabetes, chronic kidney disease, arterial hypertension) as suggested in the report by Zhou and colleagues [14], and, for this reason, we felt that everyone should be hospitalised in a semi-intensive care unit to enable close monitoring and prompt management of possible complications and deterioration. Of note, no one was obese and 3 out of 4 has a history of previous thrombotic events (and 2 were on chronic treatment with warfarin). As per our local protocol, we are currently using high dose LWMH, also based on the recent evidences supporting a favourable course in acute in patients treated with heparin (probably due to antiviral and immunomodulating effects of the latter) [15, 16].

At least in this particular set of individuals, specific treatment for COVID-19 may pose even more problems than it solves. Lopinavir-ritonavir was never used in our cohort because of fear of drug interactions even before the NEJM evidence of lack of efficacy [17]. Hydroxychloroquine seems acceptable, but needs close EKG monitoring because of coexistent other QT enlarging drugs; for the time being, no patient showed significant QT enlargement. Systemic steroids were tapered on in all our patients, with apparent clinical benefit; we also decided in favour of the off-label use of anakinra (as part of a local-based trial) [18] and remdesivir [19] in patient 2 as a “rescue therapy”, but we are not able to draw any conclusion from these treatments because she deteriorated shortly after their initiation.

We feel one of the crucial points in this set of patients regards the possible sequelae this infection may leave on the graft; this is an unique problem for lung transplant recipients, who are at risk of developing chronic lung allograft dysfunction as a consequence of viral infection [20]. Close follow up is definitely warranted: a CT scan should probably be obtained at 45-90 days from presentation to assess resolution of GGO; pulmonary function tests, as well, may reveal initial onset of pulmonary function decline.

Is allograft dysfunction to be expected? This and other questions should prompt further research, possibly with the use of national and international registries in order to collect as many data as possible.

In conclusion, we reported four cases of COVID19 in LuTx recipients: three of them presented an apparently benign short term outcome, but one died despite optimised treatment. A strong matter of concern is if this infection is able to trigger any form of early or late allograft dysfunction. We should carefully monitor these patients and prevent further spread of infections, especially in this cohort of individuals.

### **COMPETING INTEREST**

The authors declare that they have no competing interests

### **AUTHORS' CONTRIBUTIONS**

Study concept and design: LCM, VR, FB

Acquisition of data: LCM, VR, FA

Analysis and interpretation of data: all authors.

Drafting of the manuscript: LCM, VR, FA, FB

Critical revision of the manuscript for important intellectual content: all authors.

Study supervision: FB, MN

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**Table 1 – History and baseline characteristics**

	<b>Patient 1</b>	<b>Patient 2</b>	<b>Patient 3</b>	<b>Patient 4</b>
<b>Indication for LuTx</b>	Cystic Fibrosis	Non specific interstitial pneumonia	Combined pulmonary fibrosis and emphysema	Idiopathic pulmonary fibrosis
<b>Time from LuTx at time of hospitalisation for COVID-19</b>	72 months	43 months	66 months	46 months
<b>Last FEV1 (% of predicted; % of baseline*)</b>	92%; 97%	58%; 78%	93%; 73%	75%; 96%
<b>Need of oxygen therapy</b>	None	None	Normal gas exchange at rest, need of oxygen therapy for physical activity	None
<b>Baseline IST</b>	Prednisone, tacrolimus and everolimus	Prednisone, tacrolimus and azathioprine	Prednisone and tacrolimus, (Mycophenolate discontinued from December 2019, because of recurrent upper and lower airways infections)	Prednisone, tacrolimus and azathioprine
<b>Graft dysfunction</b>	None	None	CLAD with DSA (donor specific antibodies) since 2015 (and previously received TPE, IVIG, Rituximab)	None
<b>Comorbidities</b>	Chronic kidney disease (last GFR 48 mL/min in January	Acute cellular rejection twelve months from LuTx;	Chronic kidney (last GFR 36 mL/min in February 2020);	Arterial hypertension; diabetes; regularly uses

	2020), arterial hypertension, chronic HBV infection; diabetes; several episodes of venous thromboembolisms, currently on warfarin	chronic kidney disease (last GFR 46 mL/min in February 2020), diabetes; severe osteoporosis with hip fracture in 2019); in January 2020, pulmonary embolism (since then, warfarin)	liver disease.	CPAP for OSA
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Abbreviations: LuTx, lung transplantation; IST, immunosuppressive therapy; CLAD, chronic lung allograft dysfunction; DSA, Donor specific antibodies; TPE, therapeutic plasma exchange; IVIG, intravenous immunoglobulin; GFR, glomerular filtration rate; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

\* Baseline FEV1 as defined in latest chronic lung allograft dysfunction (CLAD) guidelines. Verleden GM, Glanville AR, Lease ED, et al. *Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment. A consensus report from the Pulmonary Council of the ISHLT*. J Heart Lung Transplant, 2019 May;38(5):493-503.

**Table 2 – Gas exchange and laboratory tests.**

	Patient 1	Patient 2	Patient 3	Patient 4
<b>ABG on admission (P/F and device)</b>	376 on RA	367 on VM 40%	329 on NC 2 LPM	362 on RA
<b>Highest level respiratory support</b>	CPAP, PEEP 7.5 cmH <sub>2</sub> O, FiO <sub>2</sub> 21%	NIMV, PSV, PS 8 PEEP 8, FiO <sub>2</sub> 95%	CPAP, PEEP 7.5 cmH <sub>2</sub> O, FiO <sub>2</sub> 35%	CPAP, PEEP 10 cmH <sub>2</sub> O, FiO <sub>2</sub> 21%
<b>ABG on discharge/last available * (P/F and device)</b>	390 on RA	70 on NIMV	311 on RA	386 on RA
<b>Laboratory test (Admission; Discharge/last available*)</b>				
<b>CRP</b> (< 0.5 mg/dL)	4.88; 1.91	5.17; 17.27	3.92; 1.26	6.76; 2.18
<b>PCT</b> (0.02 – 0.06 µg/L)	0.10; 0.03	0.25; 0.49	0.16; 0.18	0.06; 0.09
<b>IL6</b> (0-10 ng/L)	29.9; NA	65; 20.6	18.6; 20.4	58; 74.2
<b>Ferritin</b> (15-150 µg/L)	151; 258	1156; 33162	163; 140	156; 281
<b>D-Dimer</b> (< 500 µg/L)	223; 423	1094; 2550	903; 838	4331; 914
<b>Fibrinogen</b> (165-350 mg/dL)	464; 564	293; 439	300; 289	515; 362
<b>Leukocytes</b> (4.8 – 10.8 10 <sup>9</sup> /L)	5880; 5640	7550; 8220	10880; 13900	3070; 5420
<b>Lymphocyte count</b> (1.20 – 3.40 10 <sup>9</sup> /L)	580; 1670	450; 40	1980; 3930	520; 850
<b>Days to apyrexia</b>	10	6	2	9
<b>Anti-inflammatory treatment**</b>	HCQ, IV MP	HCQ, IV MP, anakinra	HCQ, IV MP	HCQ, IV MP
<b>Anti-microbial treatment***</b>	Piperacillin/tazobactam	Piperacillin/tazobactam	Piperacillin/tazobactam	Piperacillin/tazobactam

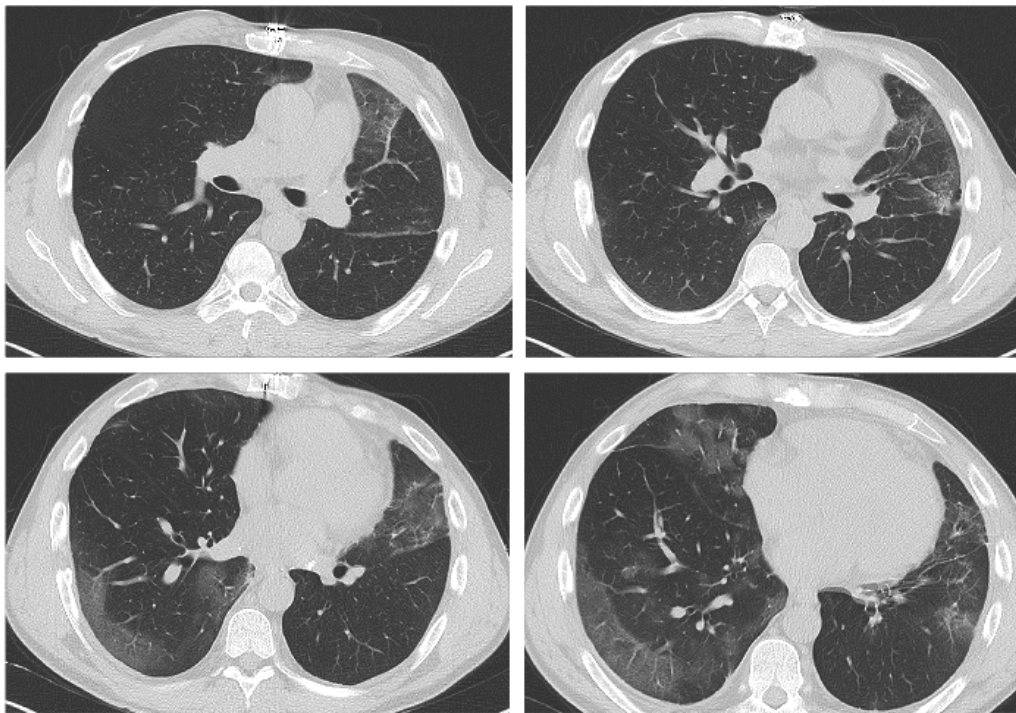
	+ levofloxacin	>> meropenem Voriconazole Remdesivir	+ doxycycline >> meropenem	
<b>Length of stay</b>	12	33	39	15
<b>Status</b>	Alive, discharged	Dead	Alive, discharged	Alive; discharged

Abbreviations: ABG, arterial blood gases; ARF, acute respiratory failure; P/F, PaO<sub>2</sub>/FiO<sub>2</sub> ratio; RA, room air; VM, VenturiMask; NC, nasal cannula; CPAP, continuous positive airway pressure; NIMV, non invasive mechanical ventilation; LPM, litres per minute; PSV, pressure support ventilation; PS, pressure support, PEEP, positive end expiratory pressure, HCQ, hydroxychloroquine; IV, intravenous; MP, metilprednisolone

\*For patient 1,3 and 4 data reported are those at discharge (D); for patient 2 we reported the last data available (LA) before death.

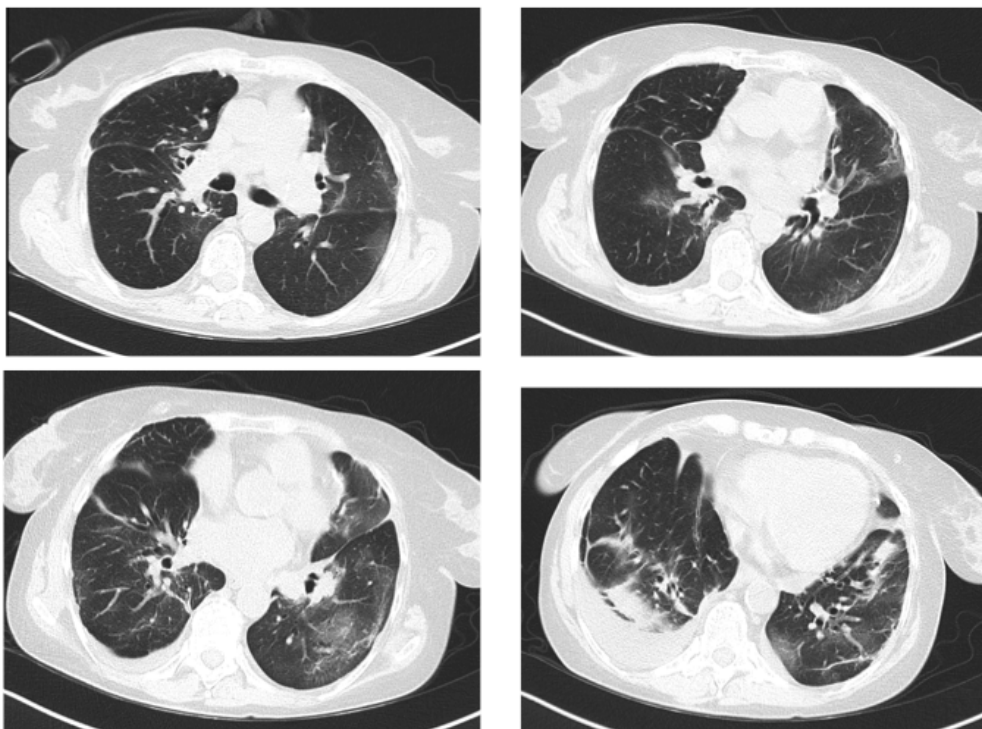
\*\*HCQ dosing, as per our local protocol: loading dose of 400 mg b.i.d. for the first 24 hours; then 200 mg b.i.d.; maximum 14 days course

\*\*\* Antimicrobial treatment dosing based on current GFR



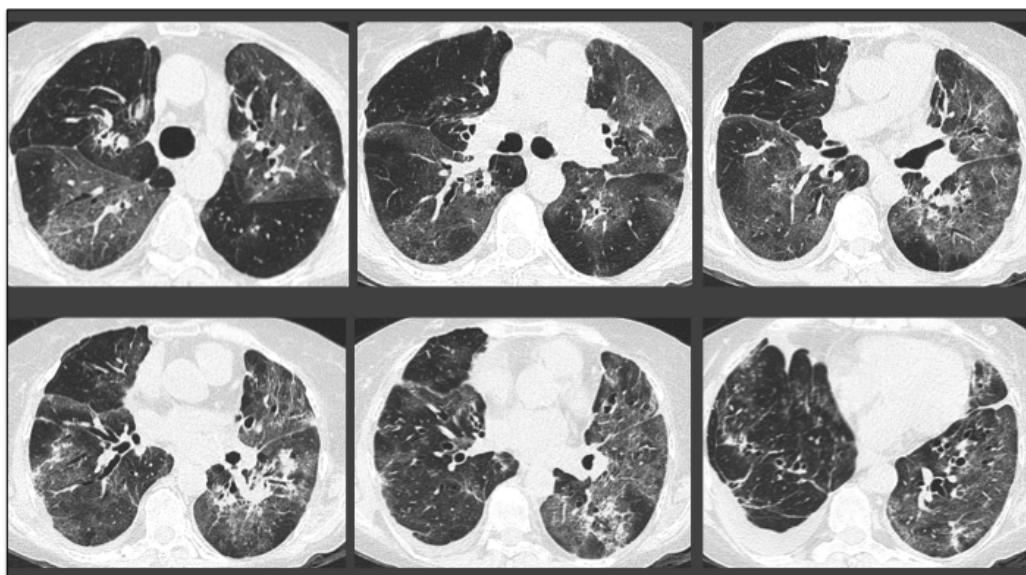
**Figure 1** – CT scan from patient 1

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**Figure 2A** – CT scan from patient 2 on admission

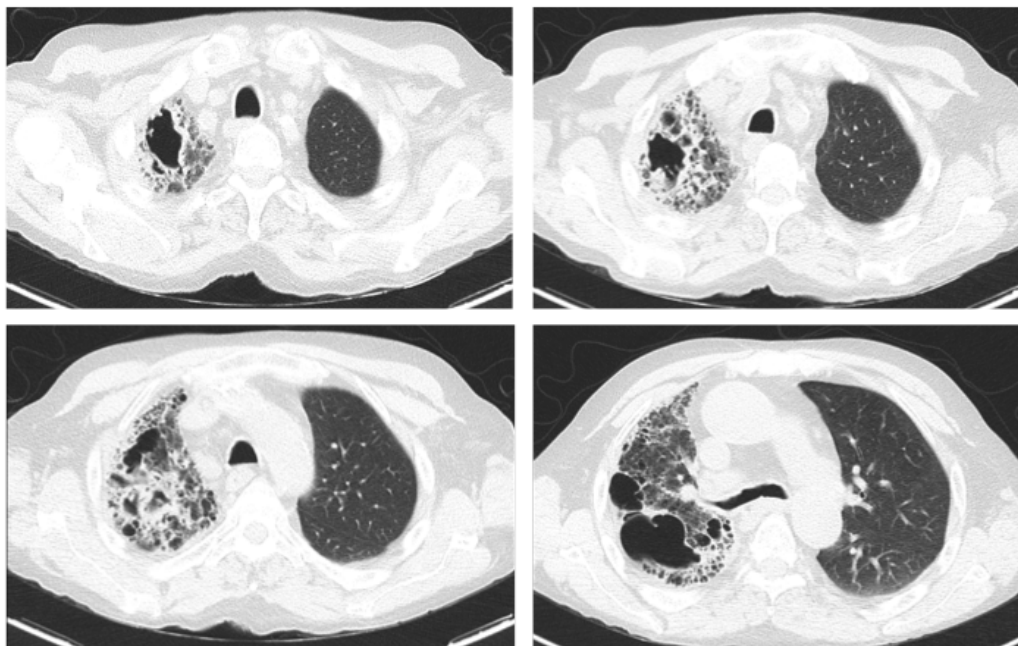
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**Figure 2B** – CT scan from patient 2 after ten days

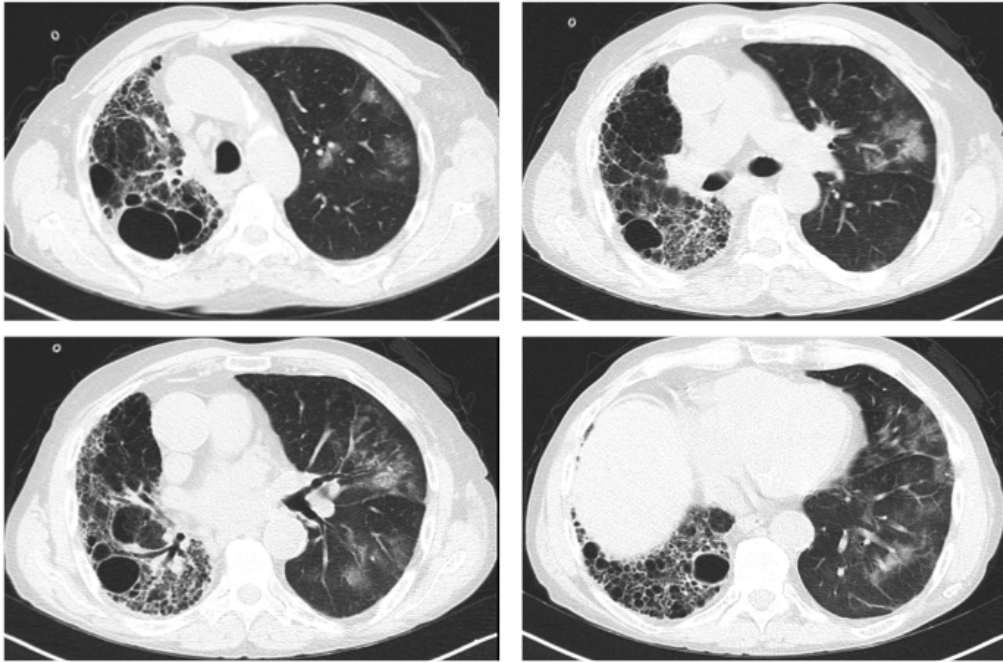
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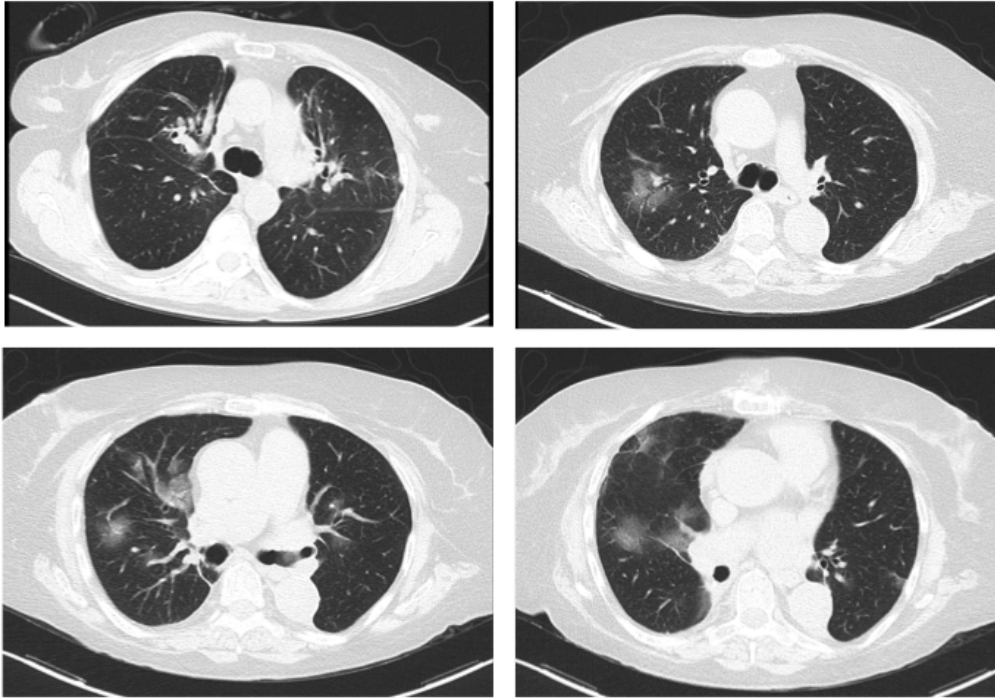
**Figure 3A** – CT scan from patient 3 on admission

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**Figure 3B** – CT scan from patient 3 after diagnosis of COVID19

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**Figure 4** – CT scan from patient 4

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