POST COVID 19 FIBROSIS

Vahan Moradians MD
Internist Pulmonologist
IRAN University of Medical Sciences
Tehran 1400-8-14

The single biggest threat to man's continued dominance on the planet is the virus.

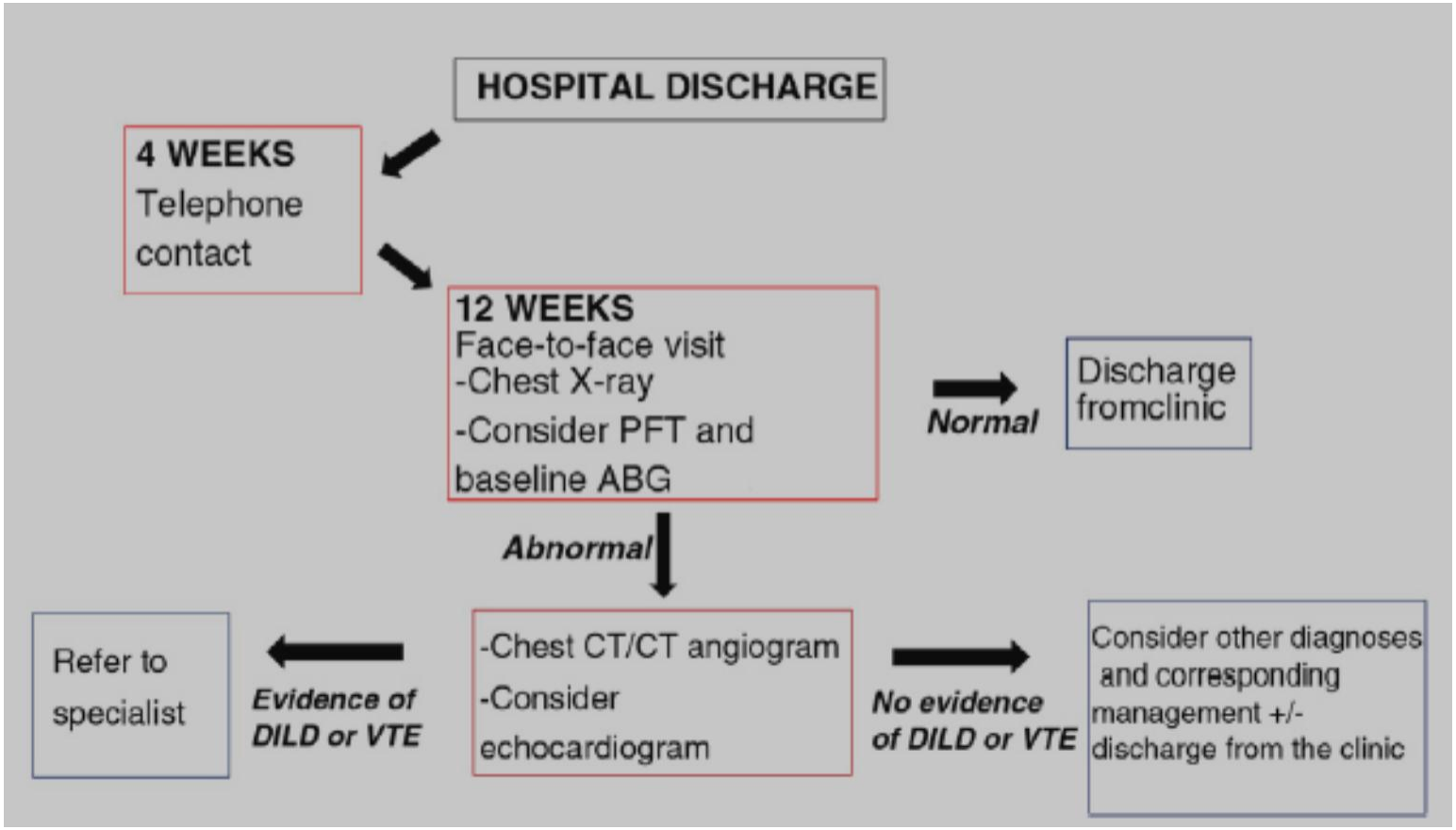
Joshua Lederberg

American molecular biologist

1925-2008

- Most of the patients who overcome the SARS-COV-2 infection do not present complications and do not require a specific follow-up, but a significant proportion (especially those with moderate/severe clinical forms of the disease) require clinical-radiological follow up.(~6%)

- Although there are hardly any references or clinical guidelines regarding the long-term follow-up of post-COVID-19 patients, radiological exams are being performed and monographic surveillance consultations are being set up in most of the hospitals to meet their needs.



- Proposal for outpatient follow-up of post-COVID-19 patients who required admission for severe pneumonia

DILD: diffuse interstitial lung disease;

VTE: venous thromboembolic disease;

ABG: arterial blood gas;

PFT: pulmonary function test.

severe pneumonia

- first telephone assessment is recommended four weeks after hospital discharge. Subsequently, at 12 weeks, a face-to-face assessment is preferable with a follow-up chest X-ray.

mild/moderate pneumonia

- the first assessment should be at 12 weeks following the schedule described above.

Pulmonary function tests (PFTs)

- 47% had a decrease in the diffusing capacity of the lungs for carbon monoxide (**DLCO**) after discharge, this being directly proportional to the severity of their pneumonia.
- D-dimer level can be an effective predictor of impaired DLCO.
- These data are consistent with what was observed in the follow-up in **2003** of patients with **severe acute respiratory syndrome** (SARS), in whom impaired DLCO was found in 15.5%---43.6% of the cases.

- Another less common abnormality is the decrease in total lung capacity (TLC), in other words, pulmonary restriction.

Table 1. Modified proposal for the definition of acute and long COVID

Acute COVID-19	Signs and symptoms of COVID-19 for up to 4 weeks
Ongoing symptomatic COVID-19	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks
Post-COVID-19 syndrome	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis
Long COVID	Long COVID describes signs and symptoms that continue or develop after acute COVID-19; it includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)

Post-COVID-19 consequences and sequelae

- A significant proportion of patients who survive acute SARS-CoV-2 infection go on to suffer a deterioration in their health.
- Respiratory symptoms persist in more than half of patients after hospital discharge, particularly those who had to be treated in ICU, and those discharged but requiring home oxygen therapy.

- Renal, cardiac, neurological, gastrointestinal, ocular and psychological complications have all been described.

Table 1 Clinical and radiological characteristics of the post-COVID-19 patients reviewed (8-12 weeks after hospital discharge with abnormal chest X-ray).

Clinical and radiological features	n (59)
Gender (%)	
Male	73
Female	27
Age (years)	
Mean	64
Range	(43–88)
Standard deviation	9
Invasive mechanical ventilation during admission (%)	
Yes	35
No	65
Chest X-ray findings (%)	
Reticular opacities/peripheral atelectasis	88
Ground-glass	61
Incomplete inspiration	25
CT findings (%)	
Bronchial dilation	80
Subpleural bands	78
Subpleural interstitial involvement (not honeycomb)	66
Ground-glass	58
Trapped air	51
Pneumatoceles	14
Honeycomb	7
Distribution of the main finding (%)	
Bilateral	98
Peripheral	98
Upper fields	66
Middle fields	93
Lower fields	86
Qualitative severity (%)	
Mild	19
Moderate	51
Severe	30

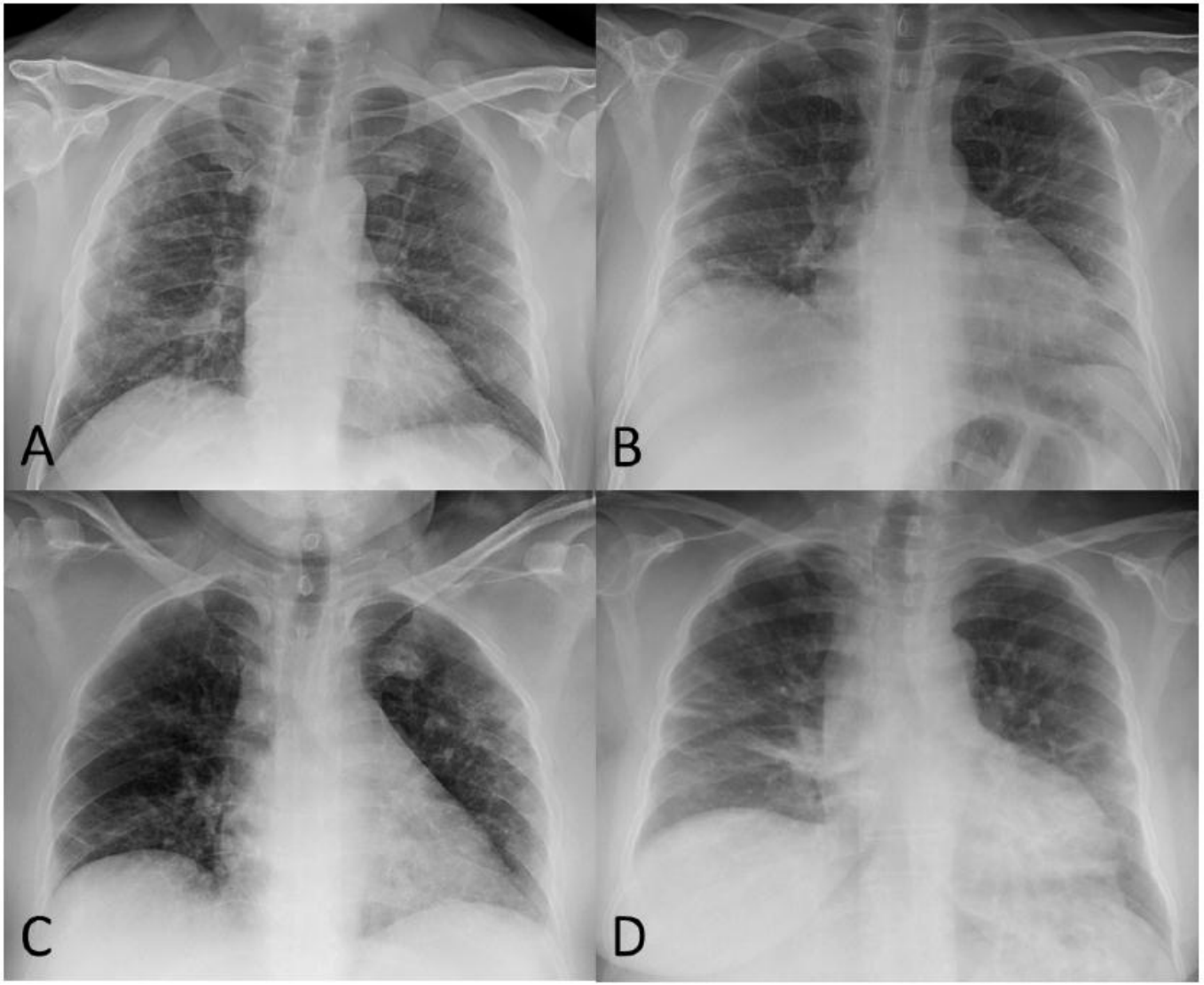


Figure 2 A) 52-year-old male post-COVID-19 whose follow-up chest X-ray shows subpleural reticular opacities, more evident in the right lung. B) 51-year-old male post-COVID-19 whose chest X-ray shows significant volume loss in both lungs and residual involvement in the form of linear subpleural opacities in the right lung. C) 56-year-old female post-COVID-19 whose follow-up chest X-ray shows a loss of volume in both lungs, peripheral laminar atelectasis in the right lung and some subpleural ground-glass opacities in the left upper lobe. D) 58-year-old female post-COVID-19 whose follow-up chest X-ray shows bilateral basal bandöpacities in relation to laminar atelectasis.

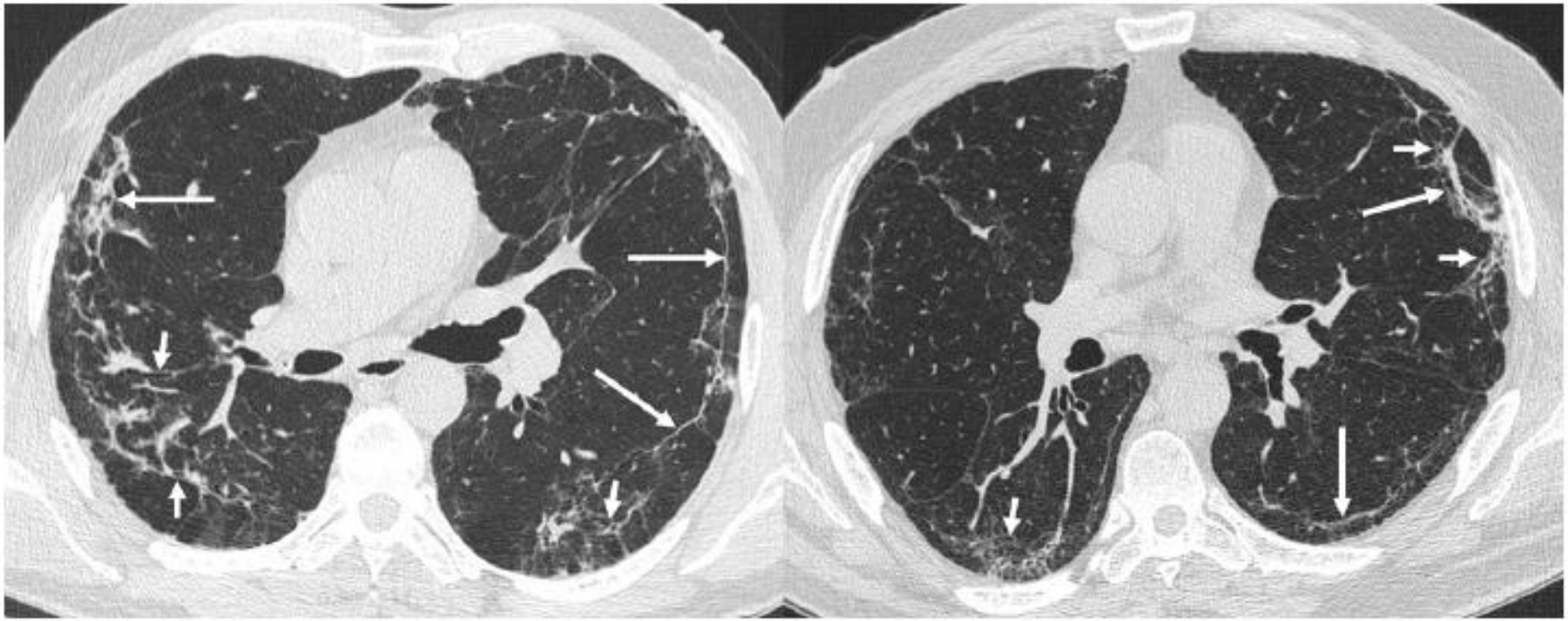


Figure 3 The most common findings on chest computed tomography (lung parenchyma window) in post-COVID-19 patients with radiological sequelae are sub-pleural parenchymal bands (band opacities and sub-pleural lines , long arrows) with distortion of the lung architecture and secondary bronchial dilation (short arrows).

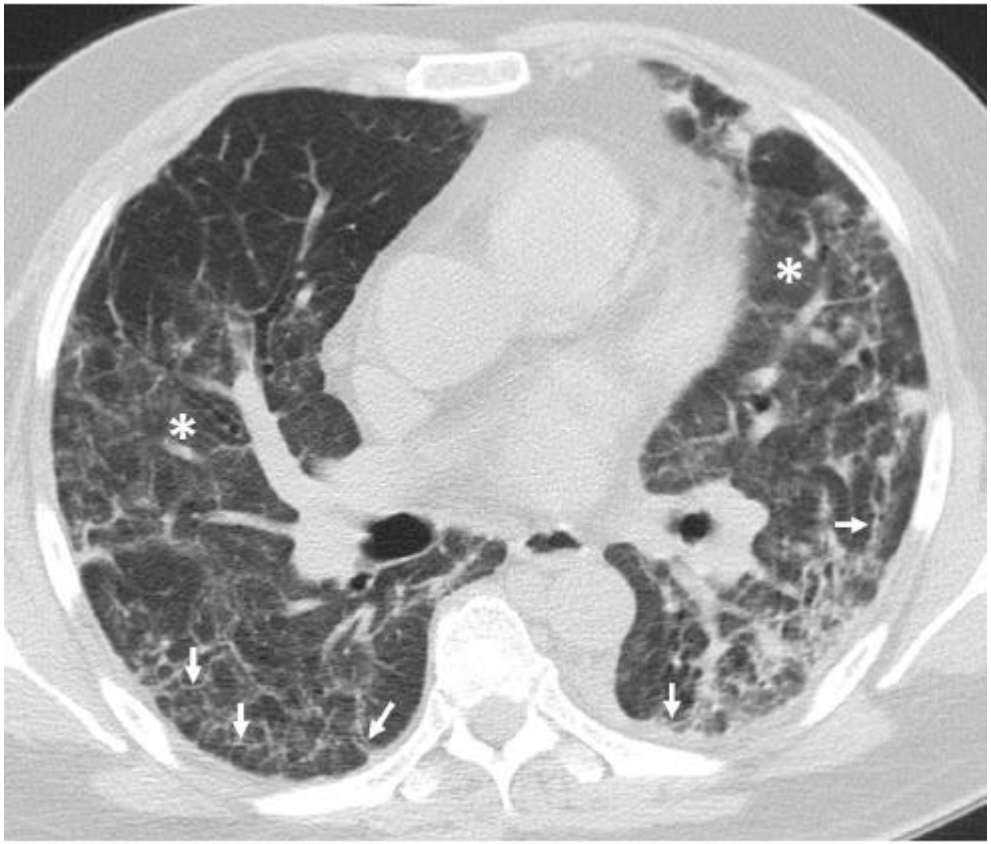


Figure 4 Chest computed tomography (lung parenchyma window) in a post-COVID-19 patient showing bilateral ground-glass opacification (asterisks) associated with coarse sub pleural reticulation (arrows).

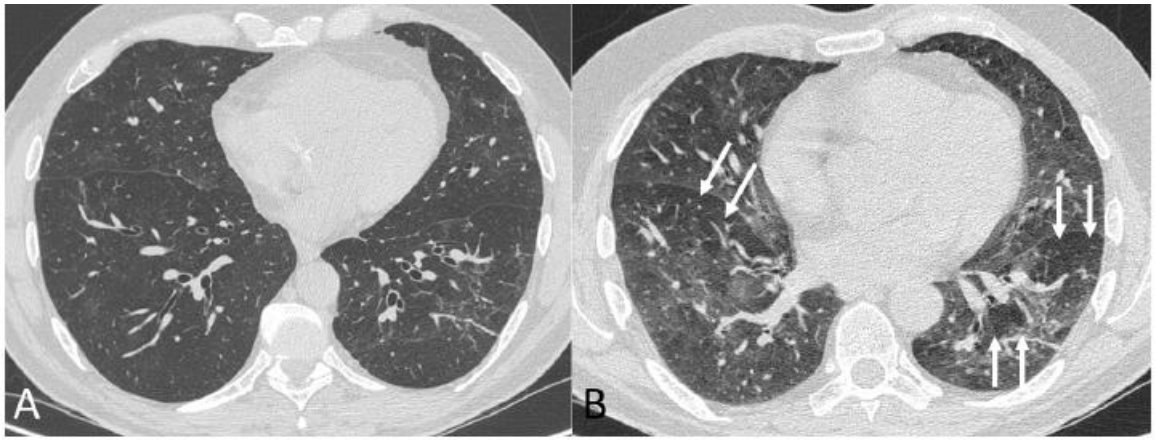


Figure 5 Chest computed tomography (lung parenchyma window) in inspiration (A) and expiration (B) in a post-COVID-19 patient with dyspnoea. In the expiratory phase of the study (B) a mosaic pattern is revealed (arrows). This pattern, which means the presence of areas of trapped air, is barely perceptible in the inspiratory phase.

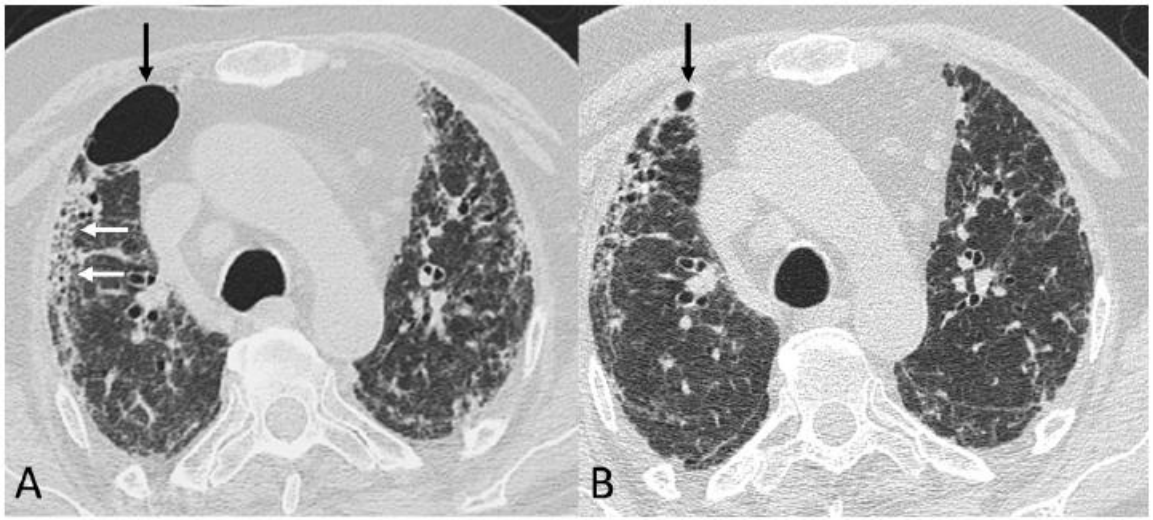


Figure 6 Chest computed tomography (lung parenchyma window) in a post-COVID-19 patient. A) A study from early June 2020 shows a pneumatocele (black arrow), bilateral coarse subpleural reticulation and areas of honeycombing (white arrows). B) In a follow-up study 8 weeks later, the pneumatocele (arrow) has significantly decreased in size.

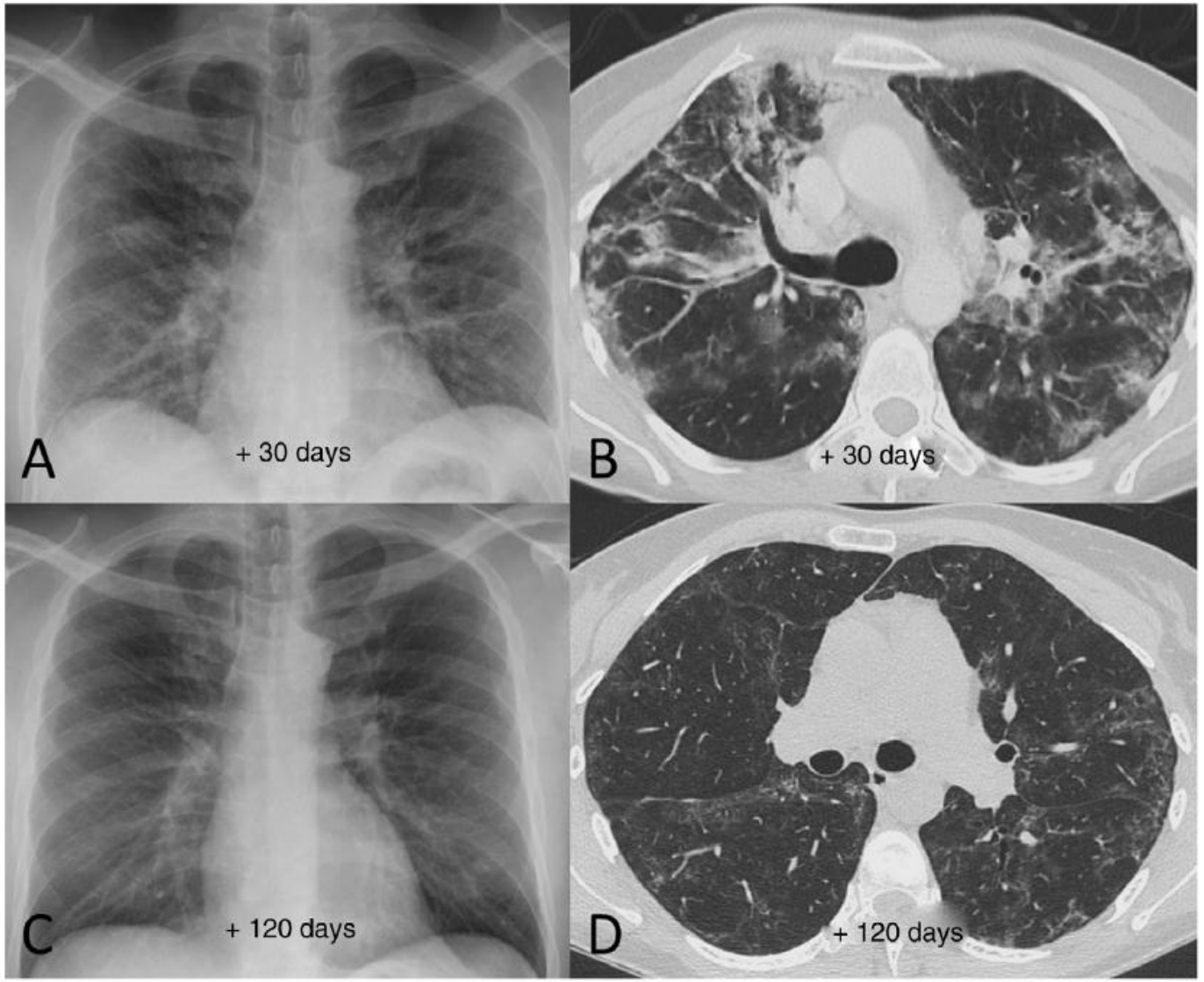


Figure 7 Example of good radiological recovery in terms of chest X-ray and computed tomography findings (lung parenchyma window) in a 45-year-old man with severe SARS-CoV-2 pneumonia after hospital discharge. A and B) Radiological tests 30 days after the onset of symptoms show patchy consolidation along with areas of ground-glass opacification and loss of volume. C and D) Radiological tests 120 days after onset of symptoms show radiological improvement with resolution of the consolidation and a reduction in the extension of the ground-glass opacification, with persistence of slight peripheral reticular interstitial involvement.

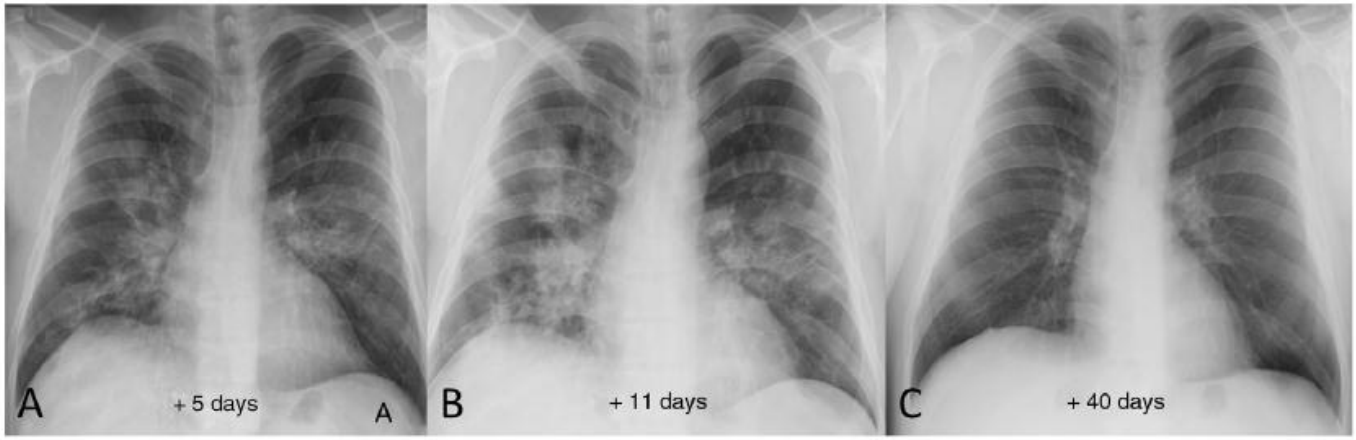


Figure 8 Example of good radiological recovery on chest X-ray in a 39-year-old male patient. A) Five days after the onset of symptoms, bilateral opacities can be seen, predominantly perihilar. B) 11 days after the onset of symptoms, radiological worsening is identified (greater density and extension of the opacities). C) Once discharged from hospital, follow-up chest X-ray 40 days after onset of symptoms shows complete radiographic resolution of the lung opacities.

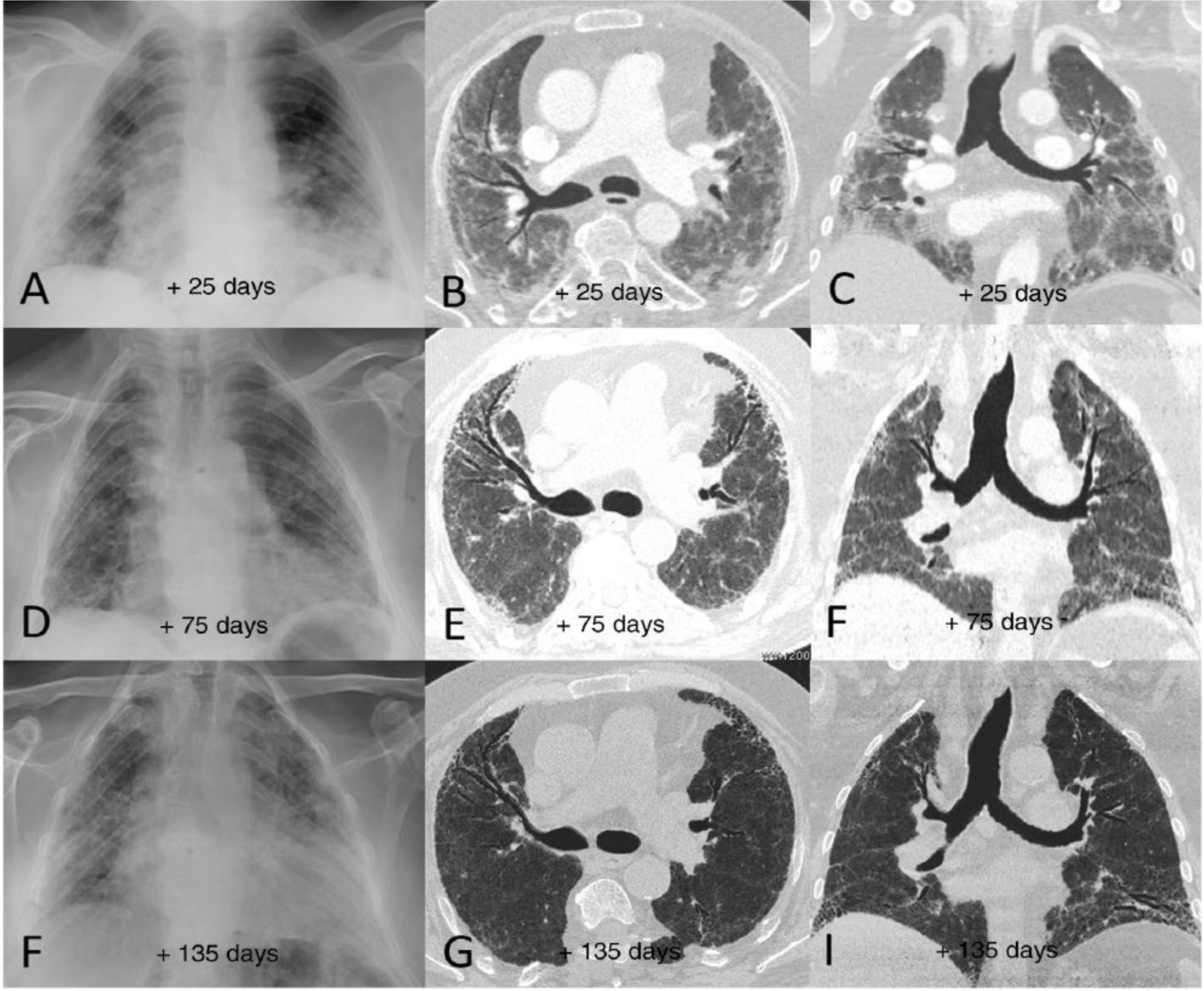

A
+ 25 days
B
+ 25 days
C
+ 25 days
D
+ 75 days
E
+ 75 days
F
+ 75 days
F
+ 135 days
G
+ 135 days
I
+ 135 days

Figure 9

- Example of poor radiological outcome in a 65-year-old male patient who required hospital admission due to SARS-CoV- 2 infection and invasive mechanical ventilation for more than 15 days.
- The patient was finally discharged after 90 days in hospital, requiring home respiratory support and having significant limitations performing basic daily activities.

- **(A---C)** Radiological tests performed 25 days after the onset of symptoms (7 days after extubation) show peripheral patchy parenchymal opacities predominantly in both middle and lower lung fields.

- **(D---F)** The tests 75 days after the onset of symptoms showed slight radiological improvement of the opacities, with an architectural distortion detected in the computed tomography consisting of incipient areas of sub-pleural reticulation and bronchial dilation, mainly in the anterior segments of both upper lobes and in the left lower lobe.

- **(G---I)** In the radiological follow-up 135 days after the onset of symptoms, the findings have barely changed with respect to the previous study (persistence of areas of sub-pleural reticulation and bronchial dilation).

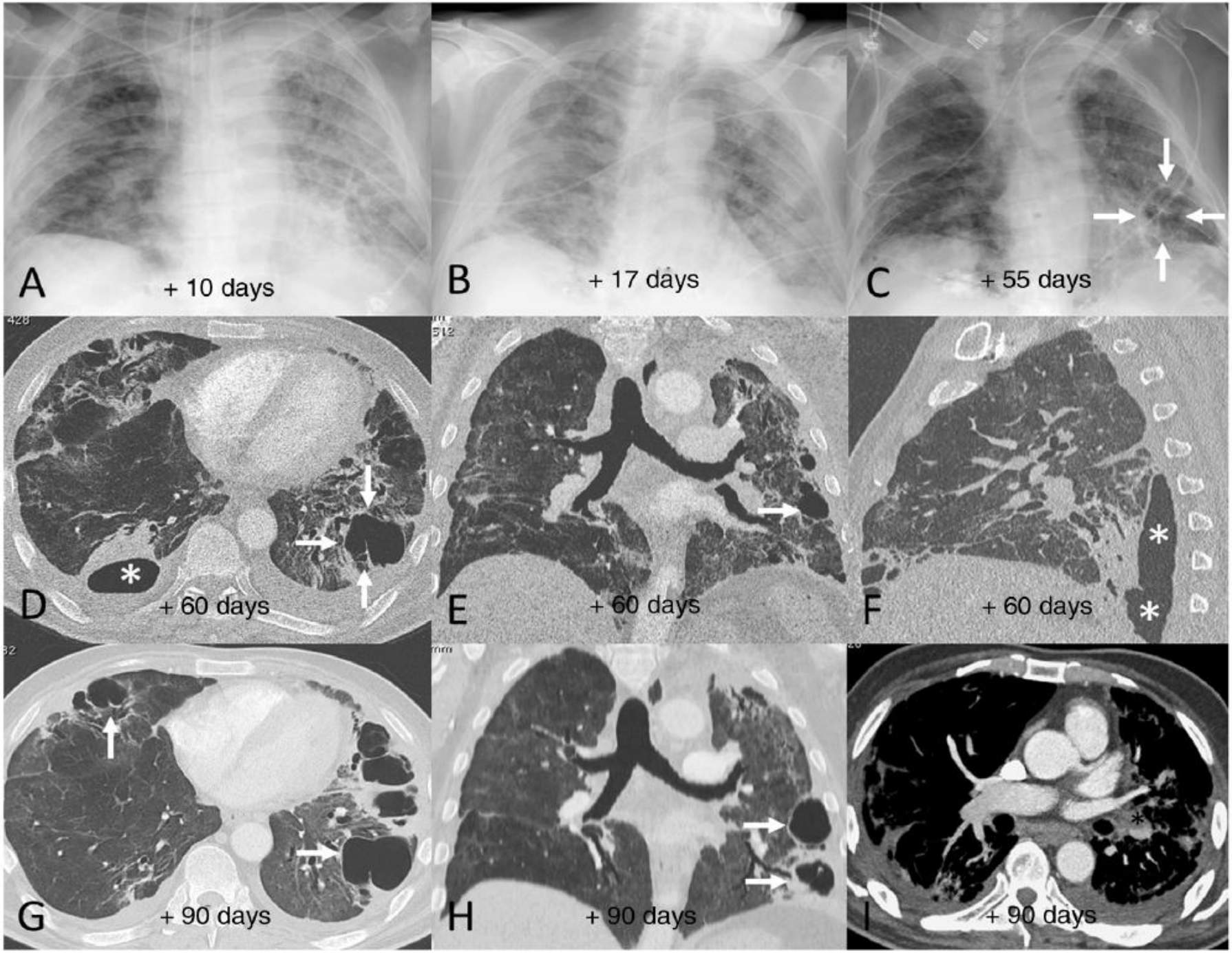

A
+ 10 days
B
+ 17 days
C
+ 55 days
D
+ 60 days
E
+ 60 days
F
+ 60 days
G
+ 90 days
H
+ 90 days
I
+ 90 days

Figure 10 Example of poor radiological outcome in a 62-year-old male patient who required hospital admission due to SARS-CoV-2 infection and invasive mechanical ventilation for 12 days. After 90 days in hospital, the patient was discharged requiring long-term home oxygen therapy and needing rehabilitation. A–C) Chest X-rays corresponding to days 10 (A), 17 (B) and 55 (C) after the onset of symptoms showing extensive persistent bilateral opacities, which are beginning to resolve by the end of the hospital stay. Note the appearance of areas of lower density in the lung bases in relation to pneumatoceles (C, arrows). D–F) Chest computed tomography (CT) images 60 days after the onset of symptoms, in which extensive bilateral fibrotic lesions in the form of subpleural bands and bronchial dilation can be seen, in addition to peripheral air cysts compatible with pneumatoceles (arrows) in the right middle lobe and both lower lobes. One of the lesions in the right lower lobe is in contact with the pleural space, causing a hydropneumothorax (D and F, asterisks). G–I) Chest CT images 90 days after the onset of symptoms, showing a slight improvement in the fibrotic lesions but slightly more growth of the pneumatoceles in the right middle lobe and left lower lobe (arrows). Note the incidental detection of an eccentric filling defect in the left lower lobe artery (I, asterisk) consistent with a subacute pulmonary embolism.

- Data from previous coronavirus infections such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERSA) , as well as emerging data from the COVID-19 pandemic, suggest there could be substantial fibrotic consequences following SARS-CoV-2 infection.

- **Diffuse alveolar damage**, which is the defining feature of ARDS, has been the characteristic histological feature in fatal COVID-19 cases with the added observation of **microvascular thrombosis.**

- In China, early reports indicated that 20% of COVID-19 cases have a severe course that requires hospitalization, and quarter of these hospitalized patients need intensive care admission

- A recent global literature survey showed that among the hospitalized patients with COVID-19,
  - about one third of cases (33%) develop ARDS,
  - a quarter (26%) require transfer to ICU,
  - 1/6 (16%) receive invasive mechanical ventilation,
  - for patients transferred to an ICU, nearly three quarter (75%) have ARDS .

- Pulmonary fibrosis is a recognized sequelae of ARDS. Its pathogenesis was previously described in other coronavirus infections and was explained by **1**-viral-induced lung injury, **2**-immune response, **3**-activation of a repair process by fibro-proliferation.

- This repair process can result in the repair of affected lung parenchymal or may lead to pulmonary fibrosis with architectural distortion and irreversible lung changes .
- So, pulmonary fibrotic changes occur early in the acute stage of infection as an attempt of repair following pulmonary injury.

- The same changes occur in COVID-19 infection leading to potential increase in the risk of occurrence of pulmonary fibrosis.

Image analysis

- **CT severity score**

1. ground-glass opacity (GGO),
2. consolidation,
3. crazy-paving pattern,
4. Septal thickening,
5. pulmonary fibrosis

- giving score (0–4) for 0, 25, 50, and ≥75% involvement, respectively, with the sum representing the total severity scores for the whole lung (0–20).

- According to the presence of fibrosis on follow-up CT after discharge, patients were classified into two groups and assigned as the :

“non-fibrotic group” (without evident fibrosis)

“fibrotic group” (with evident fibrosis).

- the number of affected segments was significantly higher in the fibrotic group ($p<0.001$).

- no significant differences between both groups as regards the distribution and location of the lesions.

- Pure GGO was statistically higher in the non-fibrotic group, while pure consolidation or GGO with consolidation , crazy paving, air bronchogram, and fibrotic changes were significantly higher in fibrotic groups ($p<0.001$).

- Patients in the fibrotic group were older than those in the non-fibrotic group

- The LOS and the percentage of ICU admission in the fibrotic group was higher than in the non-fibrotic group

- In comparison with both groups in **laboratory studies** including
  - lowest **lymphocyte level**,
  - C-reactive protein (**CRP**) level,
  - serum **ferritin**,
  - high-sensitivity **troponin**,
  - **D-dimer**,

- there was a statistically significant difference between both groups ($p < 0.001$) with higher serum levels detected among the fibrotic group.

- **Age** of the patients,
- initial CT **severity score**,
- **consolidation/crazy-paving score**,
- **ICU admission**

- were independent risk factors associated with the presence of post-COVID-19 fibrosis ($p<0.05$)

- COVID-19 patients, **cardiac troponin** is a prognostic marker with a strong association with mortality observed in the currently available reports of patients hospitalized with COVID-19, with some evidence suggesting cardiac troponin T/I even as an **independent predictor of mortality**.

Table 2 Comparison of particular characteristics between the groups on peak CT imaging

Characteristic		Non-fibrotic group (109), *N* (%)	Fibrotic group (101), *N* (%)		*p* value
Number of affected segments		9.69 ± 3.13 5–16	15.12 ± 2.91 8–22	*t* test 13.0	<0.001
Location	Upper lobe	53 (48.6%)	45 (44.6%)	*Z* test 0.45	0.65
	Middle lobe or lingula	78 (71.6%)	80 (79.2%)	*Z* test 1.12	0.26
	Lower lobe	85 (78.0%)	87 (86.1%)	*Z* test 1.35	0.18
Distribution	Central	10 (9.2%)	9 (8.9%)	*Z* test 0.17	0.86
	Peripheral	65 (59.6%)	74 (73.3%)	*Z* test 1.94	0.05
	Central and peripheral	34 (31.2%)	28 (27.7%)	*Z* test 0.40	0.69
Opacification	Pure GGO	56 (51.4%)	20 (19.8%)	*Z* test 4.61	<0.001
	GGO with consolidation	30 (27.5%)	47 (46.5%)	*Z* test 2.71	0.007
	Pure consolidation	23 (21.1%)	34 (33.7%)	*Z* test 1.89	0.06
	Bronchiectasis	3 (2.8%)	8 (7.9%)	*Z* test 1.37	0.17
	Crazy paving	66 (60.6%)	87 (86.1%)	*Z* test 4.01	<0.001
	Air bronchogram	48 (44.0%)	73 (72.3%)	*Z* test 4.0	<0.001
	Fibrosis with irregular interface, coarse reticular pattern, and parenchymal band	23 (21.1%)	63 (62.4%)	*Z* test 5.94	<0.001
	Pleural effusion	8 (7.3%)	13 (12.9%)	*Z* test 1.10	0.27

Table 3 Comparison between COVID-19 patients with and without evidence of fibrosis. Non-fibrotic group (n =109); fibrotic group (n =101)

	The studied group, N = 210		Test	p value
	Non fibrotic, N = 109	Fibrotic, N = 101		
Age (years)				
Mean ±SD	49.26±13.36	58.81±14.82	t test 4.91	<0.001
Range	18–76	24–94		
Sex				
Male	76 (69.7%)	73 (72.3%)	X^2 0.17	0.65
Female	33 (30.3%)	28 (27.7%)		
Severity score				
Mean ±SD	7.55±3.32	15.20±3.34	U 11.09	<0.001
Range	1–14	9–20		
Consolidation/crazy-paving score				
Mean ±SD	5.42±3.55	12.63±4.22	U 10.06	<0.001
Range	0–15	5–20		
Lymphopenia	64 (58.7%)	79 (78.2%)	X^2 9.2	0.002
Elevated high-sensitivity troponin	17 (15.6%)	28 (27.7%)	X^2 4.6	0.03
High ferritin levels	62 (56.9%)	81 (80.2%)	X^2 13.1	<0.001
Elevated CRP	90 (82.6%)	95 (94.1%)	X^2 6.6	0.01
Elevated D-dimer	87 (79.8%)	96 (95.0%)	X^2 10.9	0.001
Length of hospital stay				
Mean ±SD	8.56±7.03	23.26±20.89	U 8.26	<0.001
Range	1–37	2–170		
ICU admission				
No	102 (93.6%)	56 (55.4%)	X^2 40.9	<0.001
Yes	7 (6.4%)	45 (44.6%)		
Steroid				
No	27 (24.8%)	7 (6.9%)	X^2 12.3	<0.001
Yes	82 (75.2%)	94 (93.1%)		

Table 4 Multivariate regression analysis for independent risk factors for prediction of post-COVID-19 fibrosis

	SE	Wald X^2	*p* value	Odds ratio	95% CI
Age (years)	0.02	9.39	0.002	3.37	0.76–14.55
Severity score	0.12	8.95	0.003	2.38	1.18–4.41
Consolidation/crazy-paving score	0.11	1.93	0.04	1.91	0.63–4.35
Lymphocytes	0.53	0.49	0.49	0.70	0.25–1.96
High-sensitivity troponin	0.66	0.29	0.59	1.18	0.90–1.89
Ferritin	0.52	0.40	0.84	0.90	0.35–2.42
CRP	0.06	0.67	0.41	1.12	0.38–9.19
D-dimer	0.0	2.59	0.05	1.98	1.01–10.19
Length of hospital stay	0.01	0.02	0.90	1.0	0.97–1.13
ICU admission	0.69	7.82	0.005	6.77	1.77–25.88
Steroid	0.74	0.16	0.69	1.01	0.24–4.28

- Initial features predictive of fibrotic-like abnormalities at 6 months were also independent predictors in multivariable analysis. These included :

- age,
- markers of disease severity
  - ✓ **tachycardia**,
  - ✓ hospital stay of **17 days or longer**,
  - ✓ total extent of disease at CT
- acute respiratory distress syndrome (ARDS),
- mechanical ventilation.

- The link between ARDS and fibrotic-like changes at 6 months was especially striking.
- ARDS was present in 63% of this participant subgroup but in only 8% of the remaining patients

- Despite partial regression over 6 months, it is interesting that the extent of ground-glass opacification and the total extent of disease at 6 months were the CT features correlating most strongly with the extent of fibrotic-like abnormalities at 6 months.

- Ground-glass opacification is sometimes indicative of fine interstitial fibrosis that is genuinely irreversible in chronic ILD .

- It is not unreasonable to hypothesize that regression of ground-glass opacification at least partially reflects remodeling of immature fibrosis.

Treatment

- **Pirfenidone** is a pyridone with a poorly understood mechanism of action and **Nintedanib** is a tyrosine kinase inhibitor.
- Although both drugs have pleiotropic effects, neither is immunosuppressive per se, and so there is no rationale for their discontinuation in the face of viral or bacterial infection.

- There remains the suggestion that nintedanib could reduce the incidence of acute exacerbation of IPF.

- Despite its efficacy, Ofev can produce side effects such as diarrhea in up to 63% of patients and increased liver enzymes in the blood, a sign of liver damage, according to clinical trial data. Most side effects are managed by either reducing the dose, interrupting the therapy, or stopping treatment altogether.

- Furthermore, after being absorbed into the bloodstream from the digestive tract, the fast metabolism of oral Ofev leaves less therapy to reach the lungs.

- To address these issues, Ofev's active ingredient — nintedanib — was reformulated as a liquid solution to be inhaled directly into the lungs. Because inhaled medicines avoid the digestive tract, this approach may reduce side effects seen in oral formulations. Moreover, fewer side effects means higher, more effective doses may be used.

- Both pirfenidone and nintedanib can be associated with hepatotoxicity, and liver dysfunction is common in patients infected with SARS-CoV-2

- **Nintedanib**, as this drug confers a theoretically increased risk of bleeding when concomitantly administered with full-dose anticoagulation. In this context, the balance of risk and benefit is likely to tip in the direction of withholding antifibrotic therapy, particularly in the acutely unwell patient with low physiological reserve

Conventional anti-fibrotic therapy in patients with IPF who are infected with SARS-CoV-2

- Pirfenidone and nintedanib are anti-fibrotic drugs that, despite having differing modes of action, are similarly effective in attenuating the rate of lung function decline by about 50%

- Wootton and colleagues found that a small proportion of patients with acute exacerbation of IPF had evidence of viral infection, including coronavirus infection (**human coronavirus OC43**).

- These drugs do not address the immune dysregulation of SARS-CoV-2 infection, nor can they be expected to attenuate the pro-thrombotic aspects of this complex pathogenic process. If anti-fibrotic therapy is to have a role, it is likely to take the form of inclusion in combination regimens, once effective anti-inflammatory treatments have been identified. Combination therapy could, in principle, address major anti-inflammatory and anti-fibrotic pathways while attenuating their fibrotic consequences.

The efficacy of anti-fibrotic therapy in different pulmonary fibrotic disorders

- These trials potentially suggest that anti-fibrotic therapy, when used early in SARS-CoV-2 infection, might have major benefits in reducing fibrotic damage driven by immune dysregulation.

- However, to have a major impact on outcome, interventions must also address the serious issue of acute lung injury.

The potential benefits of anti-fibrotic therapy in the prevention of acute lung injury

- Putative treatment benefits with anti-fibrotic therapy in reducing the prevalence of acute exacerbations of IPF were observed in patients already established on anti-fibrotic therapy.

- The applicability of these data to COVID-19 depends on the rapidity of action of anti-fibrotic drugs and their introduction before severe acute lung injury has supervened (ie, before assisted ventilation).

- Much the same can be argued from data in small cohorts of patients with IPF undergoing resection of lung cancer, a frequent trigger of fatal acute exacerbations in IPF.

- In three Japanese studies, perioperative pirfenidone therapy was given to patients 4 weeks before surgery and for a variable time afterwards.

- Clinical outcomes were compared between patients receiving and not receiving pirfenidone, although these evaluations were neither placebo controlled nor randomised.

- Treatment with pirfenidone was associated with significant reductions in both postoperative mortality and acute exacerbations.

- In summary, we hypothesise that a clinical trial of anti-fibrotic therapy in COVID-19 before ventilation is warranted.

Novel anti-fibrotic drugs for the treatment of severe COVID-19

- A number of early anti-fibrotic studies focused on key antiviral proteins, such as IFN-β and IFN-γ. Subsequent studies have found that exogenously administered as well as endogenously produced interferon might induce pulmonary vasculopathy,

- This finding is important given that pulmonary vascular disease could play an important role in severe COVID-19 disease.

- Indeed, circulating IFN-γ and CXCL10 concentrations are raised in patients with severe COVID-19.

- There are two important issues to consider when trying to determine whether a novel anti-fibrotic drug would be harmful or beneficial in the context of SAR-CoV-2-related illness :

1. First, what is the effect of anti-fibrotic molecules on viral internalisation and replication?

2. And second, what is their effect on mitigating the cytokine storm that seems to be responsible for complications in severe COVID-19 such as ARDS?

- A major target for anti-fibrotic therapies is the TGF-β pathway. There are a number of drugs in development that target various molecules in this pathway, including :
  - those against αvβ6 integrin (BG00011 [Biogen, Cambridge, MA, USA];
    - PLN-74809 [Pliant Therapeutics, San Francisco, CA, USA])
  - galectins (TD139 [Galecto Biotech, Copenhagen, Denmark]).

- These are particularly interesting candidates because the SARS-CoV-2 spike protein contains an Arg-Gly-Asp integrin-binding domain and a number of coronaviruses contain an N-terminal galectin fold, raising the possibility that :

therapies that inhibit integrins or galectins

might be of benefit in treating COVID-19

- **IL-1**, which has been identified as a key component of the cytokine storm in COVID-19 and other viruses, might mediate its affects through **Arg-Gly-Asp binding integrins**

- Similarly, there is a well described role for galectins in viral infections.
- **Gal-3** is upregulated in lung epithelial cells after **influenza A** infection and promotes binding to **Streptococcus pneumonia**.
- Following H5N1 influenza infection, **Gal-3 knockout mice** do not have lower viral loads than control mice but do have reduced pulmonary inflammation, and **are protected** from bleomycin and TGF-β-induced lung injury and fibrosis.

- Although there is clearly much work to be done before these drugs could be considered safe, let alone beneficial in the context of COVID-19, the medical community should be reassured that there is biological rationale to suggest that anti-fibrotic therapies might have potential as novel therapeutics for severe COVID-19.

- Although the role of IL-1 in the pathogenesis of IPF is well described, and inhibiting IL-1 could possibly prevent the development of post-COVID-19 fibrosis, the role of anti-IL-6 strategies is less clear.

- Although IL-6 is generally considered to be a pro-fibrotic molecule , an experimental study with the bleomycin model of pulmonary fibrosis suggested that **inhibiting IL-6 in the early phase of lung injury promotes fibrosis** and that inhibition in the later stages of injury at the onset of the fibrotic phase might ameliorate fibrosis

- Nintedanib has been shown to attenuate broncho-alveolar lavage concentrations of IL-1β, and pirfenidone reduces serum and lung IL-6 concentrations in murine models of pulmonary fibrosis, providing further biological rationale for the use of pirfenidone in COVID-19.

	Inhibits viral infection or disease	Inhibits experimental acute lung injury	Inhibits IL-1 or IL-1 effects	Inhibits IL-6
Nintedanib	Not described	Not described	Yes[38,39]	Yes[40,41]
Pirfenidone	Not described	Yes[42]	Yes[43,44]	Yes[42]
αvβ6 integrin blockers and knockout mice	Yes[45,46]	Yes[47,48]	Yes[48]	Yes[49]
Gal-3 inhibitor and knockout mice	Yes[50,51]	Yes[51,52]	Yes[51]	Not described
Autotaxin inhibitor	Not described	Not described	Not described	Yes (skin);[53] not described
Lysophosphatidic acid inhibitor (BMS-986020; SAR100842)	No	Yes[54]	Not described	Yes (skin)[53]
JNK inhibitor	Yes[55-58]	Yes[59]	Not described	Yes
mTOR pathway modulator	Yes[60]	Yes[61]	Yes[61]	Yes[43]
SAP (also known as PTX2)	Yes[60,62,63]	Yes[64]	Not described	Not described
AT2R inhibitor	Not described	Yes[65,66]	No[44]	Yes[65]

Table: Potential link between antiviral mechanisms and antifibrotic drugs

COVID-19, ARDS, and pulmonary fibrosis

- Although many patients who develop ARDS survive the acute phase of the illness, a substantial proportion die as a result of progressive pulmonary fibrosis.

- In an autopsy study of 159 patients with ARDS, fibrosis was noted in
  - three (4%) of 82 patients with a disease duration of less than 1 week,
  - 13 (24%) of 54 patients with a disease duration of between weeks 1 and 3,
  - 14 (61%) of 23 patients with a disease duration of greater than 3 weeks.

- **Suggesting that to be effective, any potential anti-fibrotic intervention should be considered within the first week of ARDS onset.**

Covid-19 CT Chest – Temporal Changes
"Tinted" Sign