

Post-COVID-19 Infection Complication : Focus on Lung Complication

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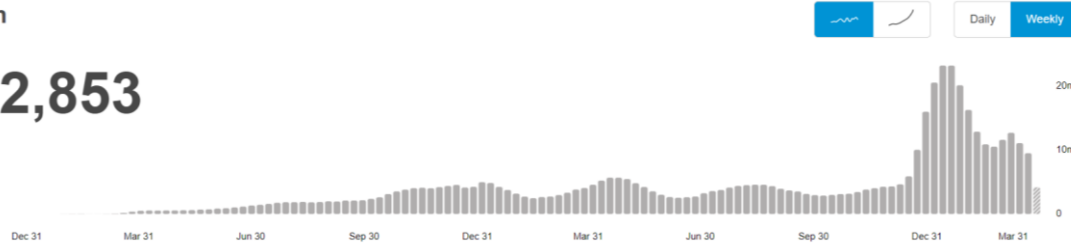
- **Post-COVID19 complication: focus on lung complication**
 - Lung fibrosis
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Epidemiology

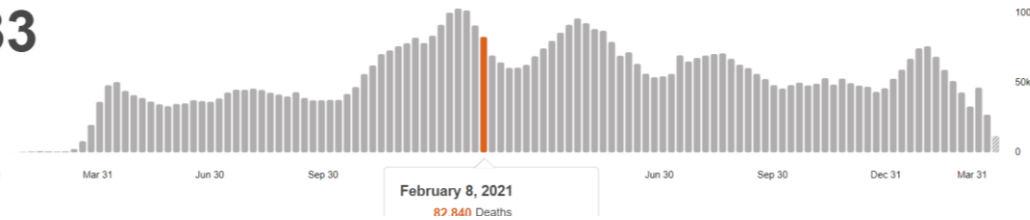
Global Situation

493,392,853
confirmed cases



6,165,833
deaths

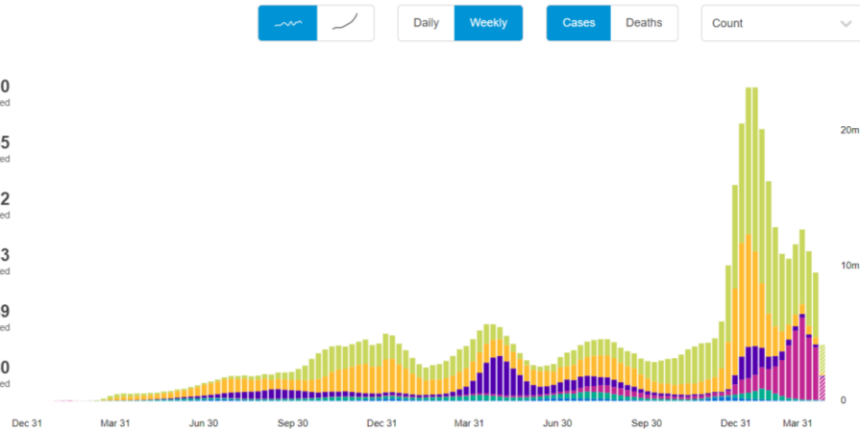
Source: World Health Organization
Data may be incomplete for the current day or week.



Situation by WHO Region

Europe	206,004,510 confirmed
Americas	151,130,255 confirmed
South-East Asia	57,310,712 confirmed
Western Pacific	48,723,983 confirmed
Eastern Mediterranean	21,615,649 confirmed
Africa	8,606,980 confirmed

Source: World Health Organization
Data may be incomplete for the current day or week.



Epidemiology



Search by Country, Territory, or Area



Covid-19 Response Fund

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WHO Coronavirus (COVID-19) Dashboard

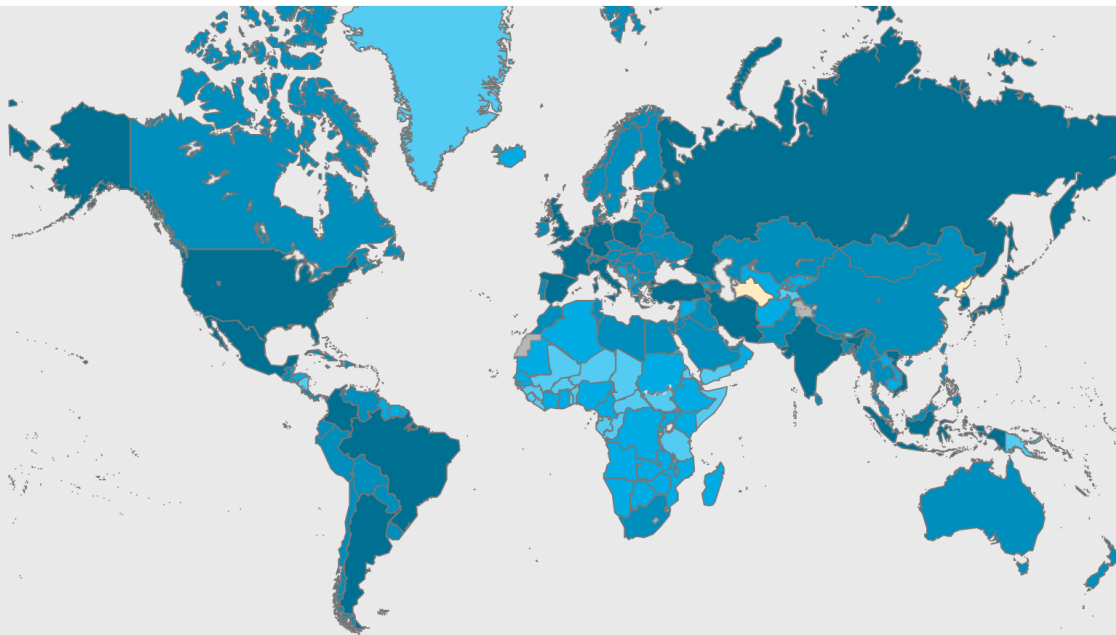
Overview

Measures

Table View

Data

More Resources



Cases

Total

1,157,995

new cases in last 24hrs

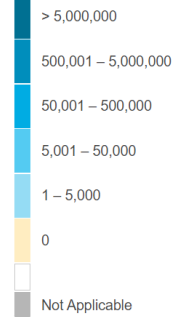
493,392,853

cumulative cases

6,165,833

cumulative deaths

Cases - Total



Download Map Data

Epidemiology



World Health Organization

Search by Country, Territory, or Area



Covid-19 Response Fund

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WHO Coronavirus (COVID-19) Dashboard

Overview

Measures

Table View

Data

More Resources



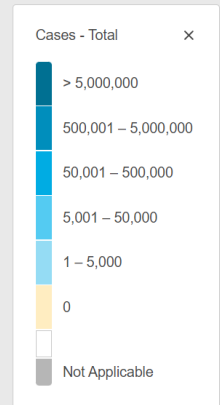
Cases

Total

1,157,995
new cases in last 24hrs

493,392,853
cumulative cases

6,165,833
cumulative deaths



Download Map Data

Pulmonary Sequelae

- A spectrum of pulmonary manifestations
 - Dyspnea (with or without chronic oxygen dependence)
 - Difficult ventilator weaning
 - Fibrotic lung damage
- Dyspnea
 - The most common persistent symptom beyond acute COVID-19
 - Ranging from 42–66% prevalence at 60–100 d follow-up
 - Median 6MWT distance was lower than normal reference values in approximately 25% of patients at 6 months
 - Prevalence similar to that in SARS and MERS survivors

Clinical Manifestation

US, hospitalized patients, 60-day outcome

- Need for supplemental oxygen or CPAP (persistent hypoxemia): 6.6~6.9%

Chopra V et al, *Ann Intern Med* 2021 Apr;174(4):576-578

Spain, 1,800 patients requiring tracheostomy

- Only 52% were successfully weaned from MV 1 month later

Martin-Villares C et al, *Eur Arch Oto-Rhi-Lar* 2021;278:1605-1612

China, 349 discharged patients

- HRCT at 6 months => at least one abnormal pattern

Huang C et al, *Lancet* 2021 Jan 16;397(10270):220-232

Pathophysiology

- Predominant mechanism of acute COVID-19
 - Direct viral toxicity
 - Endothelial damage and microvascular injury;
 - Immune system dysregulation and stimulation of a hyper-inflammatory state;
 - Hypercoagulability with resultant in situ thrombosis and macrothrombosis
 - Maladaptation of the angiotensin-converting enzyme 2 (ACE2) pathway.

Pathophysiology

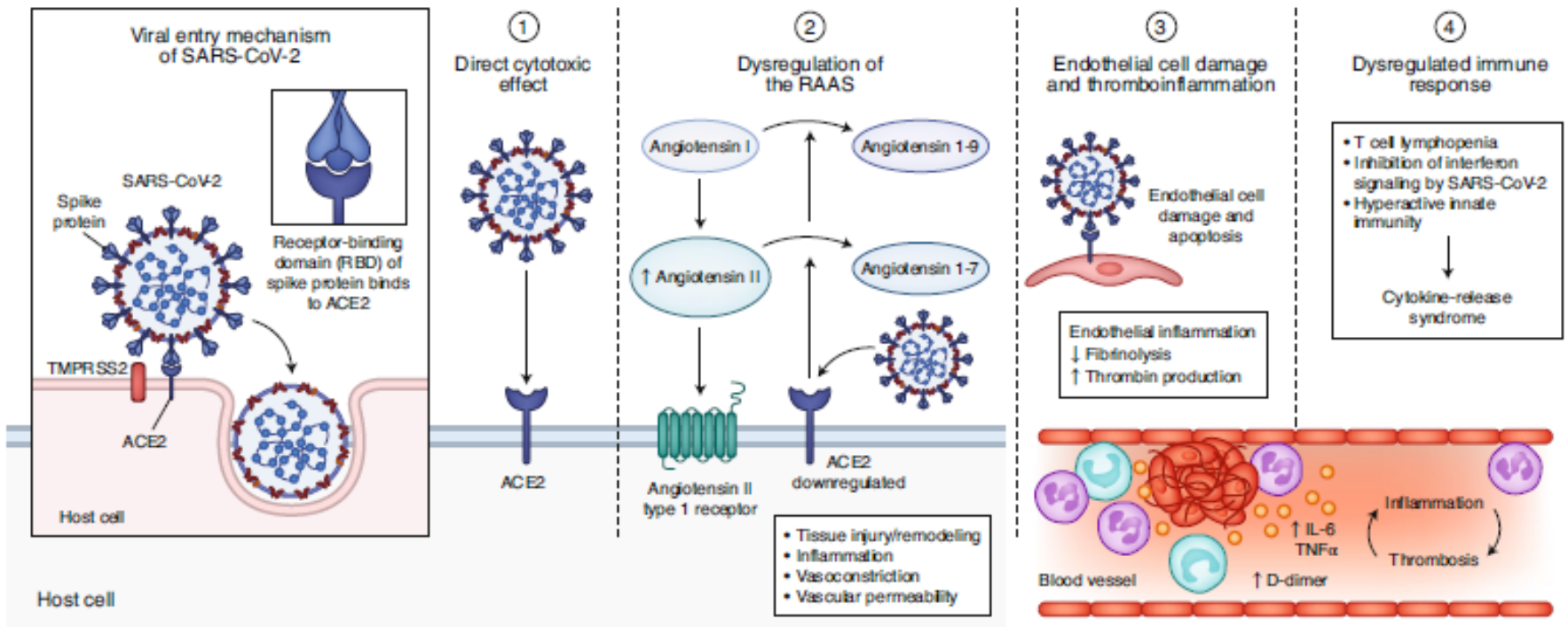


Fig. 1 | Pathophysiology of COVID-19. SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (far left). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNF α .

Long COVID

- **Acute COVID-19:** Presence of signs and symptoms of COVID-19 from onset to 4 weeks.
- **Ongoing symptomatic COVID-19:** Signs and symptoms of COVID-19 between 4 and 12 weeks.
- **Post-COVID-19:** Signs and symptoms lasting more than 12 weeks and not explained by an alternate diagnosis.
- **Long COVID-19:** Refers to the association of both ongoing and post-COVID-19

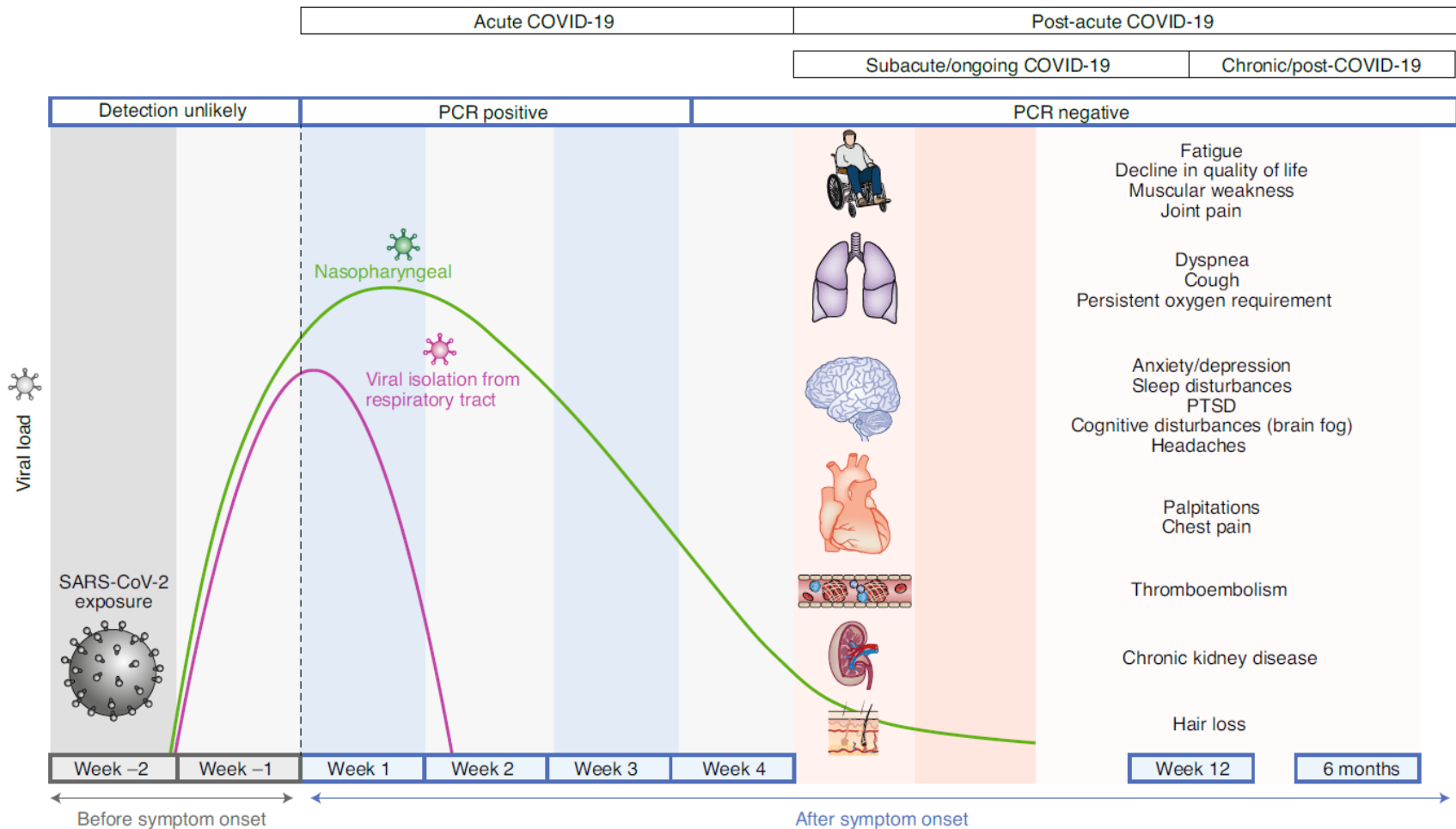
(from summary of NICE, SIGN, and RCGP rapid guideline)

Long COVID

Table 1. Proposed descriptions of long COVID.

Reference	Terms	Description
[4] [5,6,7]	Long COVID Long-hauler COVID-19 Long-COVID Chronic COVID syndrome	Long-term COVID-19 illness that is cyclical, progressive, and multiphasic. Multi-organ symptoms that persist for months after acute COVID-19.
[8]	Long-haul COVID Long-tail COVID	Symptoms lasting for > 100 days.
[9,10] [11,12,13]	Long COVID Late sequelae of SARS-CoV-2 infection Long-haulers Long-COVID	Symptoms lasting for > 2 months. Symptoms lasting for > 4 weeks after the initial infection or diagnosis.
[14]	Post-acute COVID-19 syndrome	Symptoms lasting for > 4 weeks after the first symptom onset.
[15]	Acute post-COVID symptoms Long post-COVID symptoms Persistent post-COVID symptoms	Symptoms lasting for 5-12 weeks. Symptoms lasting for 12-24 weeks. Symptoms lasting for > 24 weeks.
[16, 17,7]	Post-acute COVID-19 On-going symptomatic COVID-19 Chronic COVID-19 Long COVID Post-COVID-19 syndrome	Symptoms lasting for 1-3 months from the first symptom onset. Symptoms lasting for > 3 months from the first symptom onset.

Post-acute COVID-19



Timeline of post-acute COVID 19

Table 1 Findings from clinical studies on the prevalence of post-acute COVID-19 syndrome									
	Carfi et al. ³	Halpin et al. ²⁴	Carvalho-Schneider et al. ²¹	Chopra et al. ²⁰	Arnold et al. ²²	Moreno-Pérez et al. ²³	Moreno-Pérez et al. ²³	Garrigues et al. ²⁶	Huang et al. ⁵
Site	Italy	United Kingdom	France	United States	United Kingdom	Spain	Spain	France	China
Number of participants	143	100	150	488	110	277	277	120	1,733
Follow-up									
Duration	2 months post-symptom onset	1-2 months post-discharge	2 months post-symptom onset	2 months post-discharge	3 months post-symptom onset	2-3 months post-COVID-19 onset	4 months post-COVID-19 onset	3-4 months post-admission	6 months post-symptom onset
Mode of follow-up evaluation	In person	Telephone survey	Telephone survey	Telephone survey	In person	In person	In person	Telephone survey	In person
Baseline characteristics									
Age (years)	Mean (s.d.) = 56.5 (14.6)	Median (ward/ICU) = 70.5/58.5	Mean (s.d.) = 45 (15)	NR	Median (IQR) = 60 (44-76)	Median (IQR) = 56 (42-67.5)	Median (IQR) = 56 (42-67.5)	Mean (s.d.) = 63.2 (15.7)	Median (IQR) = 57 (47-65)
Female (%)	37.1	46	56	NR	38.2	47.3	47.3	37.5	48
Acute COVID-19 features									
Oxygen therapy requirement (%)	53.8	78			75.4				75
Non-invasive ventilation (%)	14.7	30							6
Invasive ventilation (%)	4.9	1							1
ICU care (%)	12.6	32	0		16.4	8.7	8.7	20	4
Post-acute COVID-19									
≥1 symptom (%)	87.4		66	32.6	74	50.9			76
≥3 symptoms (%)	55.2								
General sequelae									
Fatigue (%)	53.1	64	40		39	34.8		55	63
Joint pain (%)	27.3		16.3		4.5	19.6			9
Muscular pain (%)						19.6			2
Fever (%)	0		0		0.9	0			0.1
Respiratory sequelae									
Dyspnea (%)	43.4	40	30	22.9	39	34.4	11.1	41.7	23
Cough (%)	-15			15.4	11.8	21.3	2.1	16.7	
Cardiovascular sequelae									
Chest pain (%)	21.7		13.1		12.7			10.8	5
Palpitations (%)			10.9						9
Neuropsychiatric sequelae									
Anxiety/depression (%)									23
Sleep disturbances (%)					24			30.8	26
PTSD (%)		31							
Loss of taste/smell (%)	-15		22.7	13.1	11.8	21.4		10.8-13.3	7-11
Headache (%)	-10				1.8	17.8	5.4		2
Gastrointestinal sequelae									
Diarrhea (%)					0.9	10.5			-5
Dermatologic sequelae									
Hair loss (%)								20	22
Skin rash (%)									3
Quality of life									
Scale	EuroQol visual analog scale	EQ-5D-5L			SF-36	EuroQol visual analog scale		EQ-5D-5L	EuroQol visual analog scale
Decline (percentage of patients reporting or yes/no)	44.1	Yes			Yes	Yes		Yes	Yes
IQR, interquartile range; NR, not reported; s.d., standard deviation; SF-36, 36-Item Short-Form Survey.									

Symptoms among Long COVID Patients

- Fatigue (31-58%)
- Dyspnea (24-40%)
- Musculoskeletal pain (9-19%)
- Anosmia/Dysgeusia (10-22%)
- Cognitive impairment ('brain fog') (12-35%)
- Sleep disturbances (11-44%)
- Cough (7-29%)
- Chest pain (6-17%)



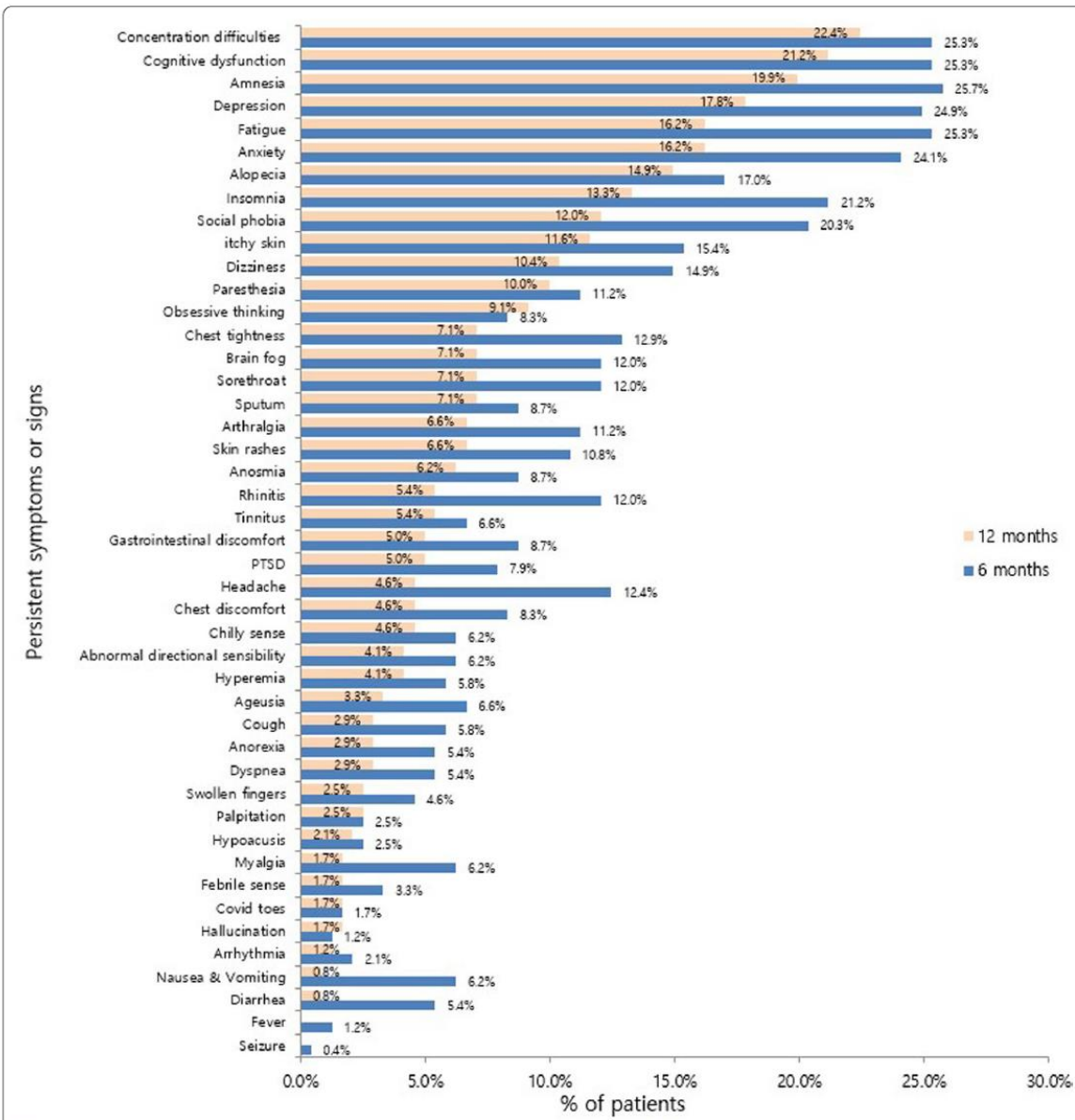


Fig. 1 Distribution of 45 persistent symptoms or signs over 12 months after acute COVID-19 infection

- 241 (female 68.0%)
- 37 [IQR 26–51] years old
- Asymptomatic:11 (4.6%)
- Mild :194 (80.5%)
- Moderate :30 (12.4%)
- Severe:6 (2.5%)
- Critical:0 (0.0%)

Lung Fibrosis

Prevalence by Definitions

China, RT-PCR positive 114 patients: ≥ 18 years
NIV : 24 pts (21.0%), MV: 4 pts (3.5%)

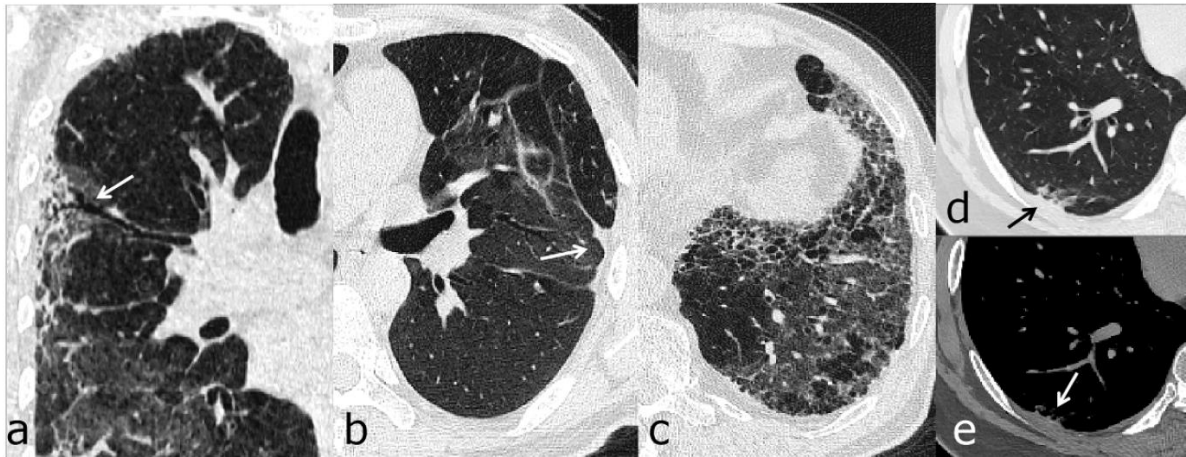


Figure 2: Chest follow-up CT findings of COVID-19 pneumonia: (a) traction bronchiectasis; (b) parenchymal bands; (c) honeycombing; (d, e) thickening of the adjacent pleura.

- **Definitions:** fibrotic-like changes: traction bronchiectasis parenchymal bands \pm honeycombing
- CT F/U: 6M
- Prevalence: 35%

Prevalence by Definitions

Italy, RT-PCR positive, 6 months, assessment by HRCT, N=118

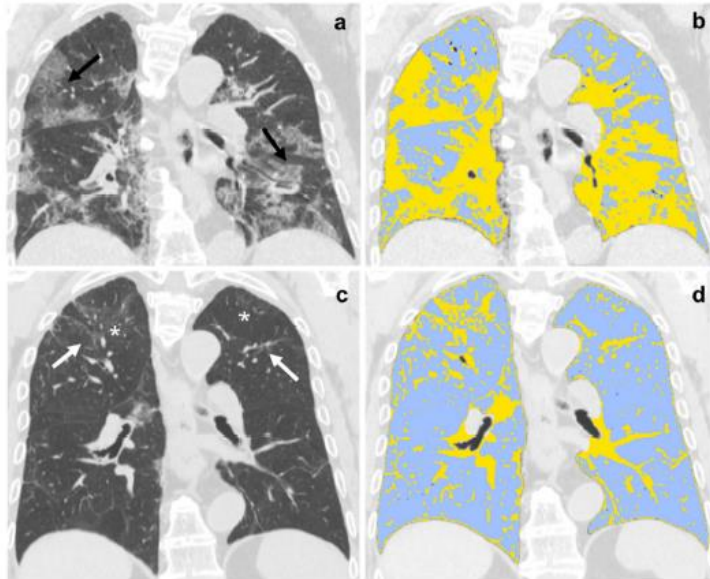


Figure 4. (a,b) Baseline and (c,d) six-month follow-up coronal thin-section unenhanced Chest CT scans of 79-year-old man, admitted to the Emergency Department presenting fever, dyspnea and cough; COVID-19 was confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing. (a) Chest CT scan shows bilateral ground-glass opacities tending to consolidation (black arrow). (b) The same scan after Quantitative Chest CT Analysis highlighted in light-blue well-aerated lung (1.5 liters, 50%) and in yellow pulmonary injury of COVID-19 pneumonia. (c) Six-month follow-up scan shows residual fibrotic-like changes (white arrows) and persisting of low-density ground glass (asterisks). (d) The same scan after Quantitative Chest CT Analysis highlighted in light-blue well-aerated lung (3.5 liters, 82%) and in yellow residual findings of COVID-19 pneumonia at six months follow-up.

- **Definitions:** fibrotic-like changes (reticular pattern and/or honeycombing)
- CT F/U: 6M
- Prevalence: 72%

Prevalence by Definitions

Netherlands, RT-PCR positive, 3 months, assessment by HRCT, N=46

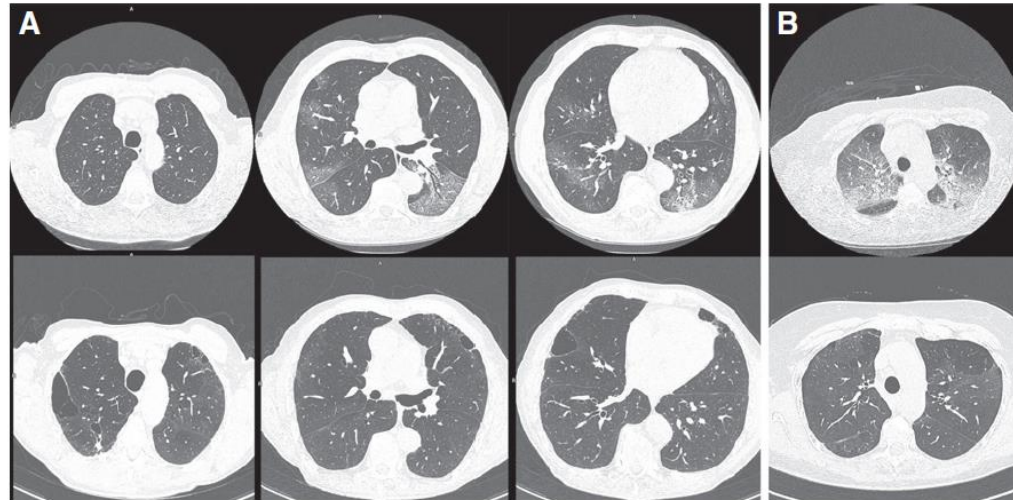
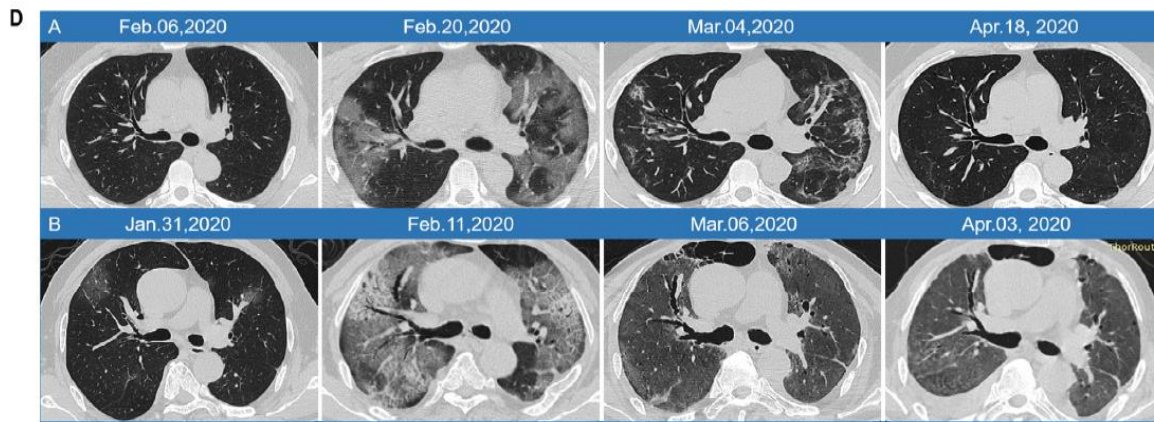


Figure 1. Representative high-resolution chest computed tomographic (HRCT) images of two of the survivors. (A) HRCT imaging performed at admission (upper row) and at 3-month follow-up (lower row). Chest computed tomographic (CT) imaging at admission shows typical bilateral subpleural ground-glass opacities. No signs of previous emphysema were detected. However, follow-up HRCT imaging shows obvious emphysematous destruction. (B) CT image at presentation at emergency department with evident ground areas with reticulation (crazy paving). Follow-up reveals diffuse areas of persistent ground glass without reticulation, as well as areas with low density in previously normal areas, possibly due to hypoperfusion.

- **Definitions:** coarse fibrous bands ± obvious parenchymal distortion BE/bronchiolectasis
- CT F/U: 3M
- Prevalence: 67%

Prevalence by Definitions

China, RT-PCR positive, Alive, 81 patients
 NIV : 21 pts (25.9%), MV: 14 pts (17.3%), ICU admission: 45 (55.6%)



- **Definitions:** parenchymal bands, irregular interfaces reticular opacities traction bronchiectasis ± honeycombing
- CT F/U: 3M
- Prevalence: 52%

Fig. 1. The clinical course and the temporal changes of follow-up CT in fibrosis and non-fibrosis groups. (A) A series of indexes on admission showed significant difference between two groups. (B) Dynamic changes of inflammatory markers including neutrophils, lymphocytes, neutrophil-to-lymphocytes ratio, eosinophils, c-reactive protein, and lactate dehydrogenase showed distinct features between two groups. (C) Oxygen supply, ICU admission, complications and treatment during hospitalization were included for comparative analysis. ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$. (D) Temporal changes in axial chest CT images of two survivors indicated the distinct evolutions of lung involvement. a) A 33-year-old male with critical pneumonia who undergone both ARDS and mechanical ventilation, discharged at March 5, 2020 with subtle linear opacities on follow-up CT. b) A 69-year-old male with critical pneumonia, undergone both ARDS and mechanical ventilation and discharged at March 1, 2020 with fibrotic pulmonary remodeling on follow-up CT. ARDS indicates acute distress respiratory syndrome.

Prevalence by Definitions

Korea, Multicenter(8), RT-PCR positive, 1 Month after discharge,
 assessment by HRCT, N=65
 ≥ 2 component: (Reticulation, Architectural distortion ± parenchymal band,
 Traction bronchiectasis/bronchiolectasis, Honeycombing)

Characteristics	number	%
Number	65	100.0%
Fibrosis (any component)	49	75.4%
Reticulation	40.0	61.5%
Architectural distortion ± parenchymal band	44.0	67.7%
Traction bronchiectasis/bronchiolectasis	47.0	72.3%
Honeycombing	11.0	16.9%
Fibrosis (≥2 component)	48.0	73.8%
Fibrosis (≥3 component)	35.0	53.8%
Underlying disease	26.0	40.6%
Emphysema	16.0	61.5%
Fibrosis (ILD)	2.0	7.7%
Bronchiectasis	3.0	11.5%
TB sequelae	8.0	30.8%

ILD: interstitial lung disease

A study on the clinical characteristics including severity of
 pulmonary fibrosis by COVID-19 (*Unpublished data*)

Lung Fibrosis: Risk Factors

- Age ≥ 65
- Illness severity
- Length of ICU stay and Mechanical Ventilation
- Smoking
- Chronic Alcoholism

Risk Factors

China, RT-PCR positive, assessment at discharge, by HRCT, N=284

Table 4. Analysis of risk factors in patients with pulmonary fibrosis.

Index	HR	95%CI	P
			value
Age(years)	1.001	0.975–1.027	0.941
High fever ($\geq 38.5^{\circ}\text{C}$)	0.502	0.174–1.450	0.203
Cough	0.708	0.309–1.621	0.708
Chest tightness	0.772	0.263–2.270	0.757
IL-6(acute stage)*	1.081	1.021–1.144	0.007
IL-6 (hospital discharge)	1.119	0.969–1.292	0.125
Lymphocyte $\times 10^9$ per L	0.921	0.711–1.194	0.536
Lymphocyte %	0.988	0.955–1.022	0.479
AST (U/L)	1.02	0.990–1.051	0.192
Albumin (g/L) *	0.821	0.734–0.918	0.001
PT (s)	0.93	0.822–1.052	0.250

Risk Factors

UK, RT-PCR positive, 6 weeks after discharge, assessment by HRCT, N=387
Established fibrosis ± ground glass abnormalities

Table 4c
In-patient ICU admission and investigations in Fibrotic and Non Fibrotic Subjects.

	No Fibrosis	Post Covid Fibrosis	P value (no. of observations)	OR (95% CI) unadjusted	OR (95% CI) adjusted
Admitted to ICU	61 (17.4%)	23 (63.9%)	<0.001* (387)	8.38 (4.02–17.46)	
Intubated	38 (10.7%)	22 (61.1%)	<0.001* (387)	12.9 (6.09–27.31)	3.48 (1.16–10.49) ^b
Duration intubated ^a (days)	14 (7–34)	27.5 (19–49)	0.004* (387)		
Peak CRP ^a (mg/L)	130.5 (70–218)	214 (122–379)	0.001* (375)		
Peak WBC ^a (10 ⁹ /L)	9.4 (7.1–13.4)	17.1 (11.9–21.3)	<0.001* (375)	6.16 (2.8–13.5) ^c	2.57 (0.85–7.79) ^b
Peak Ferritin ^a (µg/L)	906 (526–1620)	1250 (932–2735.5)	0.036 *(145)		
Peak D-Dimer ^a (ng/ml)	619 (310–2633)	3026 (1530–5467)	0.001 *(145)		
Minimum Lymphocytes ^a (10 ⁹ /L)	0.7 (0.5–1.0)	0.5 (0.4–0.8)	0.006* (375)		
High risk Inpatient CXR	136 (46.7%)	29 (85.3%)	<0.001* (325)	6.61 (2.49–17.6)	3.31 (0.82–13.33) ^b
In patient CT score ^a	14 (11–19)	21 (17–23)	0.001 * (89)		
High risk inpatient CT (score ≥18)	21 (28%)	9 (64.3%)	0.008 * (89)	4.63 (1.39–15.4)	

Data presented as Frequency (%) compared using Chi square test except.

^a Median (interquartile range) compared using Mann-Whitney *U* test * significant.

^b Adjusted for male sex, persistent breathlessness, myalgia, invasive ventilation, Peak WBC and high risk CXR during COVID-19 admission.

^c Unadjusted OR for Peak WBC ≥12 × 10⁶/L.

Risk Factors

Table 1. Associations with post-Covid PF. Abbreviations: L/O = length of, LOS = length of stay, f/u = follow-up, RR = respiratory rate, Sx = symptoms, CMs = comorbidities, pts = patients. * = compared to those with acute DAD, ** = compared to all other patterns of DAD. All associations are $p < 0.05$.

Study	N=	Criteria for Defining PF	Age	CMs	Medications	Ventilation	Labs
Yu, et al., 2020	32	Based on f/u CT; Pts put into 1 of 2 groups. Fibrosis group had evidence of fibrosis.	Older (Median 54 y.o, vs. 37)	HTN	Longer L/O steroid therapy, longer L/O antiviral therapy	-	Higher CRP, higher IL-6, lower lymphocytes
Hu, et al., 2020	76	Based on CT at discharge; Pts put into 1 of 2 groups. Fibrosis group showed presence of PF.	Older (Median 58 y.o, vs. 39)	HTN	-	-	Higher CRP, lower IFN- γ , lower lymphocytes
Huang, et al., 2020	81	Based on f/u CT; Pts put into 1 of 2 groups: PF group showed fibrotic changes.	Older (Median 63 y.o, vs. 51)	HTN	More likely to have needed steroids	Higher rate of ventilation	Higher CRP, higher D-Dimer, lower lymphocytes
Li, Y. et al., 2020	30	Based on histopathology; Samples put into fibrosing DAD, acute, or organizing groups.	Younger * (Median 64 y.o, vs. 77)	-	-	Longer ventilation **	-

Risk Factors

Korea, Multicenter(8), RT-PCR positive, 1 Month after discharge, assessment by HRCT, N=65
 ≥ 2 component: (Reticulation, Architectural distortion ± parenchymal band, Traction
 bronchiectasis/bronchiolectasis, Honeycombing)

Characteristics	Multivariable model-1		Multivariable model-2	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age >65	1.810 (0.840-3.901)	0.130		
Male gender	0.516 (0.209-1.277)	0.153	0.473 (0.204-1.098)	0.081
BMI >25	1.416 (0.636-3.154)	0.394		
P/F ratio >100	1.918 (0.855-4.303)	0.114		
APACHE score >12	2.141 (0.908-5.048)	0.082		
Creatinine >1.0	5.014 (1.770-14.203)	0.002	5.786 (2.171-15.423)	<0.001
Use of Neruomuscular blocker	0.222 (0.076-0.648)	0.006	0.197 (0.075-0.514)	0.001
Prone position	1.070 (0.448-2.554)	0.879		
ECMO	0.216 (0.073-0.641)	0.006	0.251 (0.087-0.722)	0.010

HR: hazard ratio, CI: confidence interval; BMI: body mass index, ECMO: Extracorporeal membran oxygenation; * age, sex, BMI가 보정됨

A study on the clinical characteristics including severity of pulmonary fibrosis by COVID-19 (Unpublished data)

Prognosis

- Post-COVID-19 Pulmonary fibrosis(PCPF)'s course
 - Could also be similar to other well-documented forms of post-viral PF such as those occurring after SARS/MERS/H1N1 infection

[In SARS patients]

- Post-viral parenchymal damage and functional decline mostly recovered within two years of disease onset
- CT studies of SARS-CoV-1 showed radiologic features suggestive of fibrosis in more than half of patients after an average of 37 days
- Interstitial abnormalities in only 5% of patients after 15 years' follow-up

Antonio GE et al. *Radiology* 2003;228:810–815.

Zhang P et al. *Bone Res* 2020;8:8.

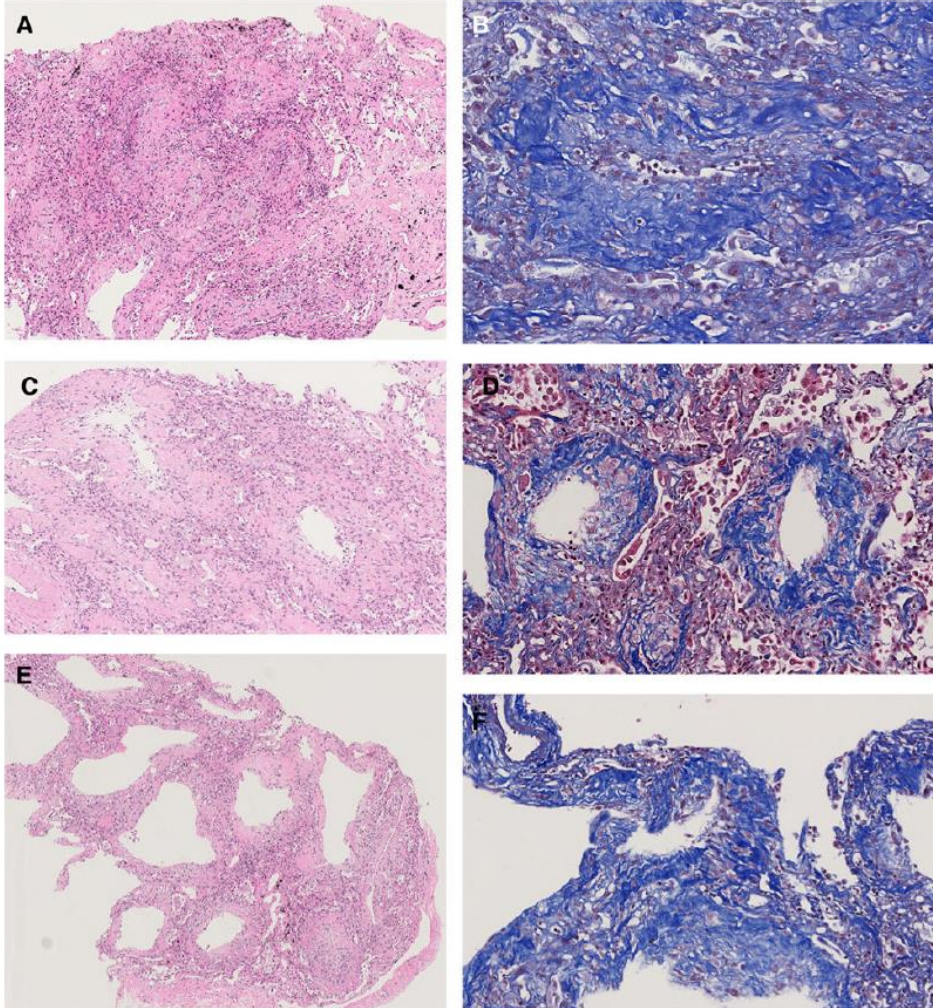
Prognosis

- It is unclear if the change in findings over time represents selection or survival bias as opposed to resolution of fibrotic imaging findings in some patients.
- Similarly, post-ARDS fibrotic changes have not been seen to progress when the etiology of ARDS is due to viral respiratory infections.

Crisan-Dabija R et al. *Proteome Res.* 2020 Nov 6;19(11):4327-4338.

Chaudhary S, et al. *Front Med (Lausanne).* 2020 Sep 9;7:539

Prognosis



N=31, died from COVID-19 infection, autopsy

- Histopathological progression of DAD to the fibrosing pattern: 43%

Prognosis

- Still much uncertainty about how PCPF may progress; as more data become available, we hope to gain more knowledge on this.
- There are currently no reliable data on the frequency and severity of PCPF may be related to difficulty diagnosing PCPF in current pandemic circumstances.

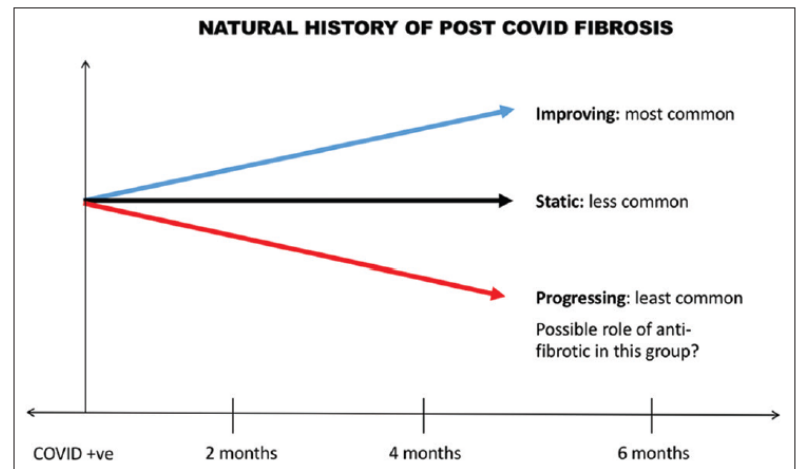


Figure 3: The natural history of post-COVID lung fibrosis is unclear with one of three possible courses. Antifibrotic may have a rationale in those who progress

Minimizing the Risk Factors

- Shortening the length of stay in the intensive care unit
- Avoiding invasive mechanical ventilation support If possible, managing the case with low airway pressure in case of forced MV
- Proper management of concomitant diseases
- Prevention of bacterial superinfections

Treatment OPTIONS

- Available evidence
- Antivirals:
 - Remdesivir (the RNA polymerase inhibitor), an antiviral agent currently approved for clinical use in treatment of SARS-CoV-2
 - Initial data have shown some promise in terms of symptom-improvement and resolution of disease in select populations, but is thought to be of greatest benefit to patients early-on in their clinical course and in those with mild-moderate disease

=> However, since it is not known if early viral clearance is protective, the role of remdesivir for fibrosis is not certain

Rochwerg B et al. *BMJ* 2020;370:1m2924

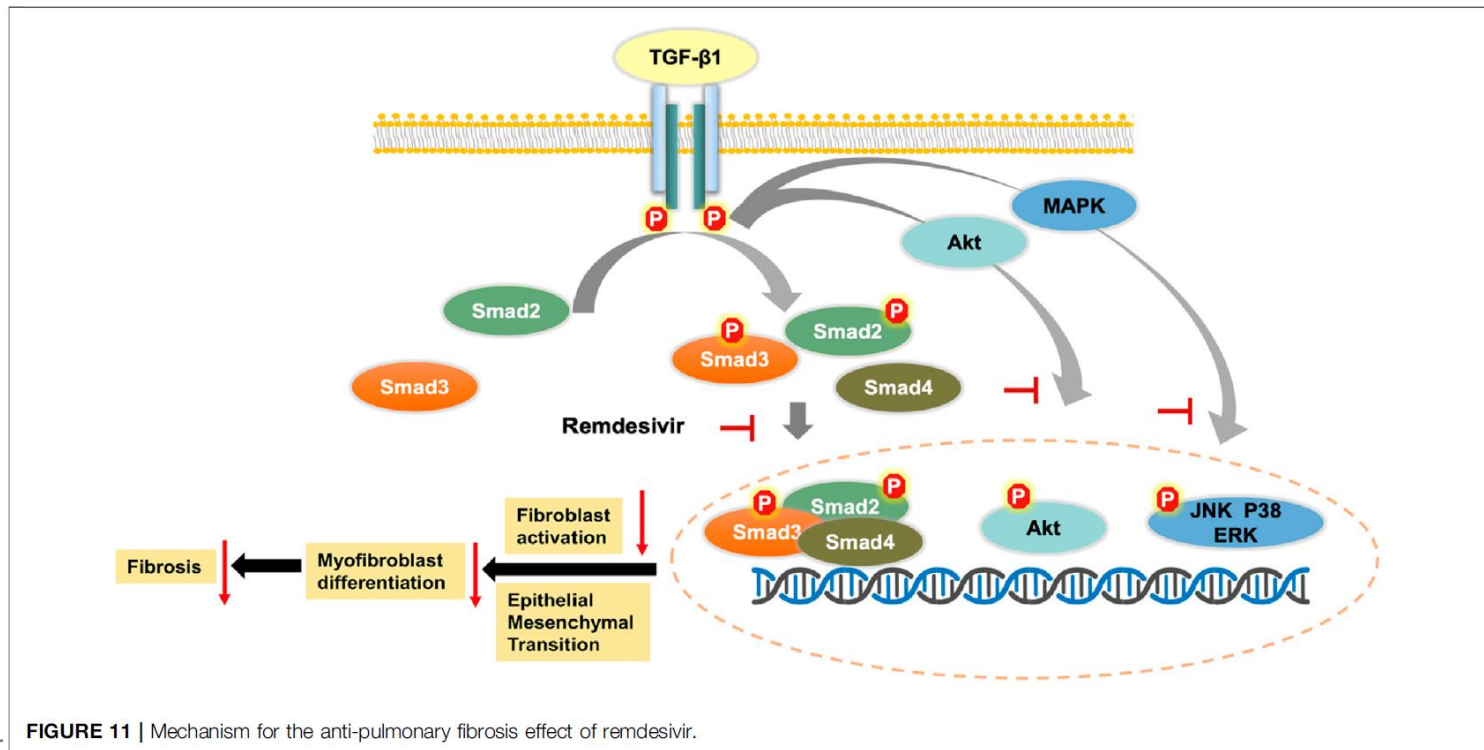
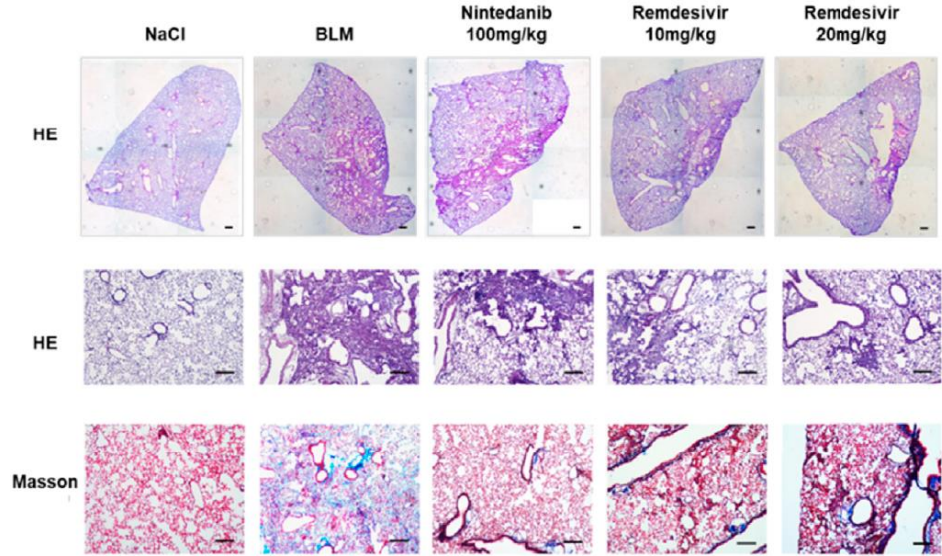
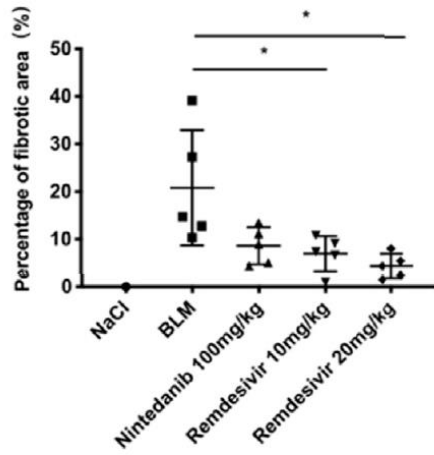


FIGURE 11 | Mechanism for the anti-pulmonary fibrosis effect of remdesivir.

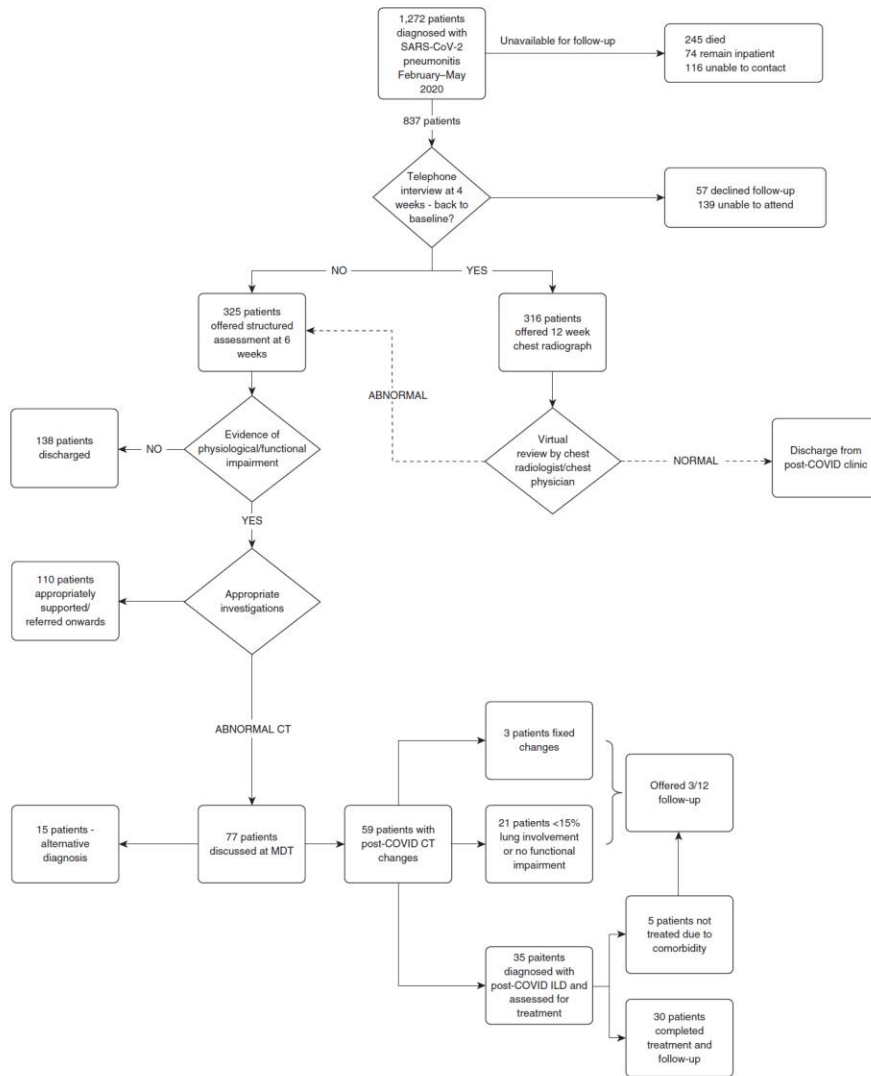
Treatment OPTIONS

- Anti-inflammatory drugs:
 - The exaggerated inflammatory response that occurs in severe COVID-19 infection has also been a target for various medications and therapies
 - The use of immunosuppressive agents is presently recommended as part of the standard treatment for COVID-19 infection
 - The RECOVERY trial has shown moderate-dose dexamethasone given for 10-days decreases the need for and the number of days on MV, reducing the risk of both immune-mediated and iatrogenic lung injury

=> insufficient evidence for long-term use in the prevention of PC-ILD

Ambardar SR et al. *J Clin Med* 2021;10:2452

Corticosteroid Treatment



- Single-center prospective observational study
- 837 pts were assessed by telephone 4 weeks after discharge
- Ongoing symptoms had outpatient assessment at 6 weeks.
- 30 pts diagnosed with persistent interstitial lung changes at a multidisciplinary team

Figure 1. Flowchart of the study population recruited between February and May 2020. COVID = coronavirus disease; CT = computed tomography; ILD = interstitial lung disease; MDT = multidisciplinary team meeting; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

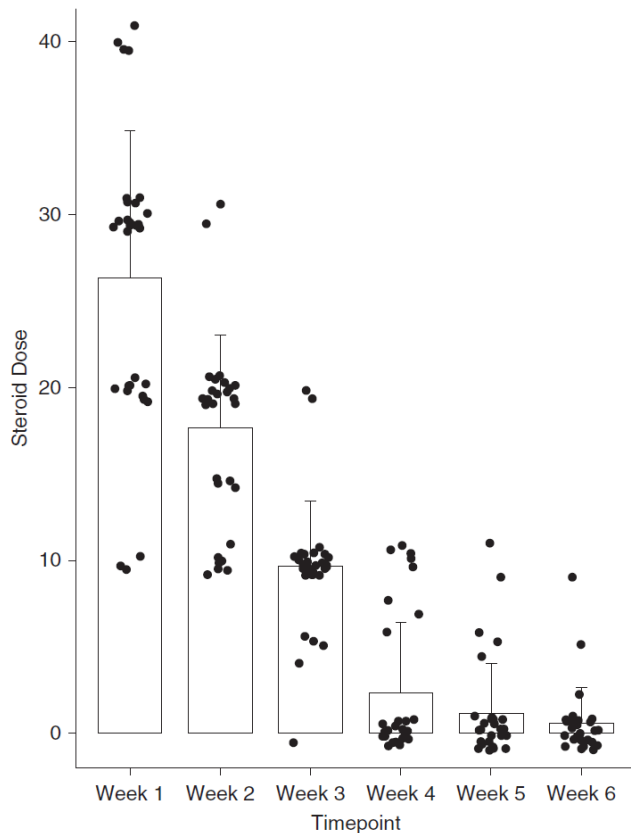


Figure 2. Steroid dosing by week. Data are presented as median and interquartile range.

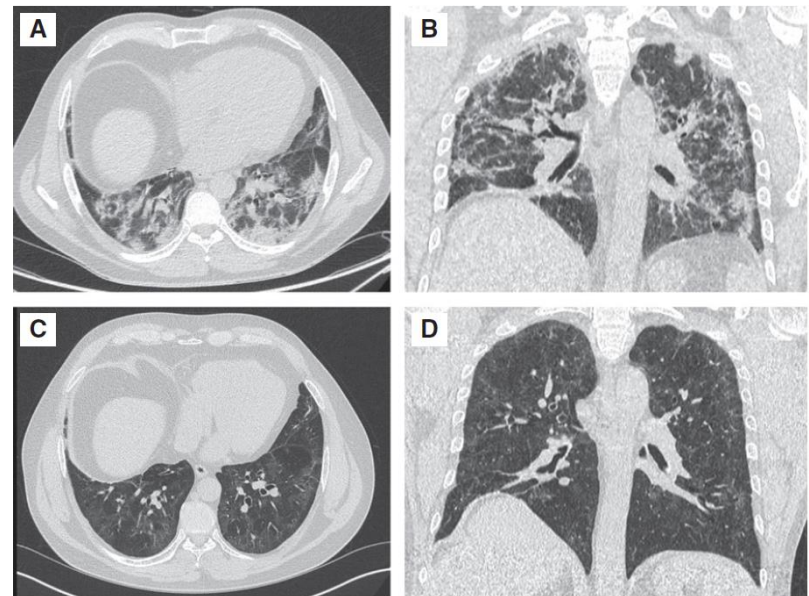
- A maximum initial dose: 0.5 mg/kg prednisolone
- The average starting dose: 26.6 mg
- Rapid wean over 3 weeks

Table 5. Follow-up data from patients with interstitial lung disease after infection with SARS-CoV-2 (n = 30)

Lung Function	Before Treatment	After Treatment	Mean Difference (95% CI)	P Value
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
TL _{CO} , SI	5.56 ± 2.56	7.05 ± 2.42	1.72 (1.18–2.25)	<0.001
TL _{CO} , %	59.7 ± 21.1	82.6 ± 15.7	22.3 (14.1–32.5)	<0.001
KCO, TL _{CO} /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

Definition of abbreviations: CI = confidence interval; FVC = forced vital capacity; KCO = transfer coefficient; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SI = International System of Units; TL_{CO} = transfer factor of the lung for carbon monoxide.

Data are presented as mean ± standard deviation unless otherwise stated.



Treatment OPTIONS

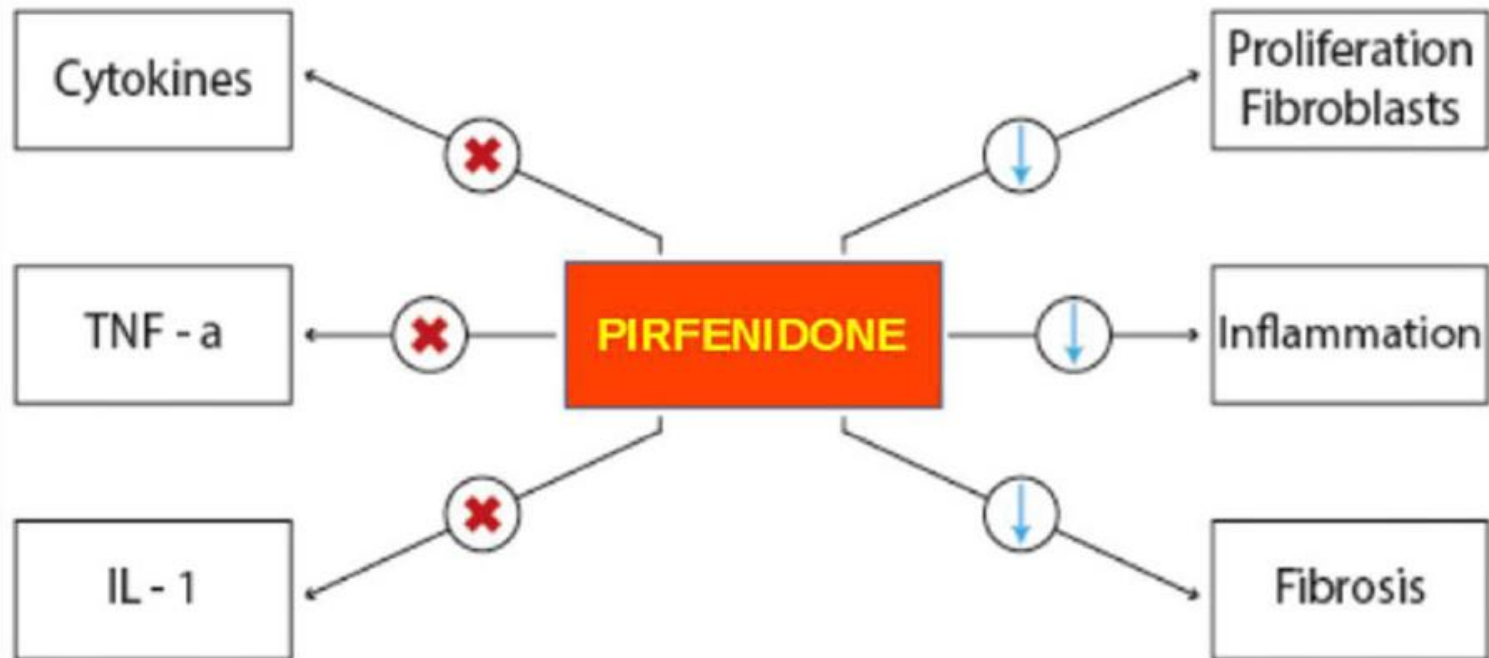
- Antifibrotics:
 - Not enough data yet
 - Lung involvement should be monitored for up to 3 months in the post- COVID period, and it should be kept in mind that there may be a possibility for regression
 - If fibrosis still persists at the end of the 12th week, there is a rationale for the use of these agents in the treatment of PC-ILD
- Pulmonary rehabilitation:
 - Vital treatment approach that can also be applied at home
 - Since PC-ILD may also cause hypoxemia, long-term use of oxygen and PR at home can help in recovery
- Other supportive treatments:
 - Risk of other modifiable risk factors that are known to increase the risk of pulmonary fibrosis
 - VLI can be reduced with adherence to lung-protective ventilation strategies, already proven to significantly reduce mortality in patients with ARDS

Antifibrotics

	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
$\alpha\beta6$ 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

Antifibrotics



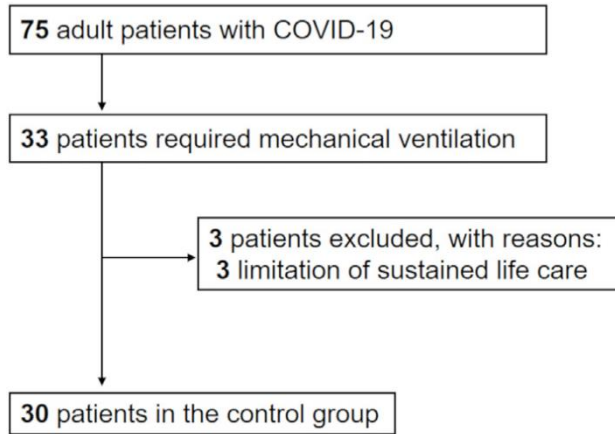
Antifibrotics

Table 2 | Active research studies and questions pertaining to post-acute COVID-19

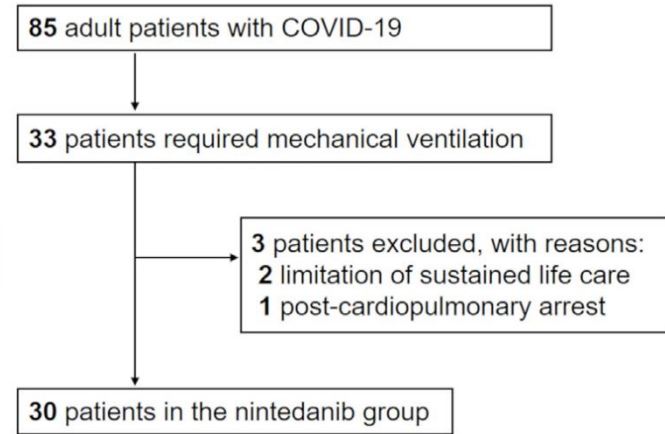
Question	Study name and/or ID ^a
General	
What are the long-term sequelae of COVID-19?	COVIDOM (NCT04679584) CO-Qo-ICU (NCT04401111) MOIST (NCT04525404) LIINC (NCT04362150) NCT04411147 NCT04573062 NCT04605757
What are the immunologic, enzymatic, metabolic and radiographic predictors of post-acute COVID-19?	BIOMARK-COVID (NCT04664023) MOIST (NCT04525404)
What are the long-term effects of COVID-19 on health-related quality of life?	COVIDOM (NCT04679584) RECOVER-19 (NCT04456036) CO-Qo-ICU (NCT04401111) COREG Extension (NCT04602260) NCT04586413 NCT04632355
What are the long-term effects of COVID-19 on functional exercise capacity?	CO-Qo-ICU (NCT04401111) COREG Extension (NCT04602260)
Pulmonary	
Is there a role for antifibrotic therapy for the prevention of development of pulmonary fibrosis and other respiratory complications in COVID-19 survivors?	NCT04652518 NCT04282902 NCT04541680 NCT04527354
Does pulmonary rehabilitation improve pulmonary outcomes in post-acute COVID-19?	NCT04649918 NCT04365738 NCT04406532 NCT04642040

Japan, RT-PCR positive, MV care
 Case: Nintedanib therapy 150 mg via NG tube from D1 to liberation of MV

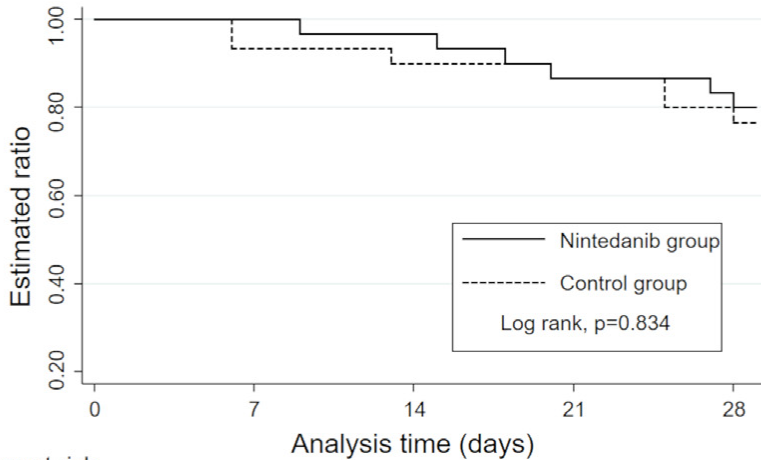
Control group
 (March to July 2020)



Nintedanib group
 (August to October 2020)

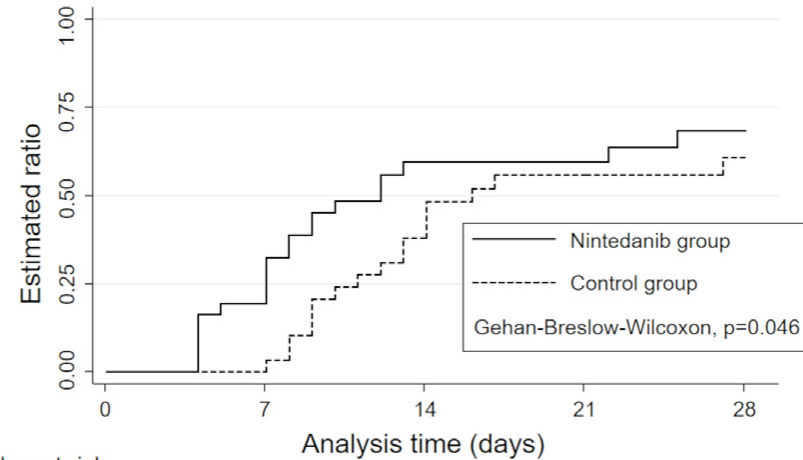


Survival



Number at risk	0	1	4	6
Nintedanib group (n=30)	0	1	4	6
Control group (n=30)	2	3	4	7

Mechanical ventilation



Number at risk	8	20	20	23
Nintedanib group (n=30)	8	20	20	23
Control group (n=30)	1	13	15	20

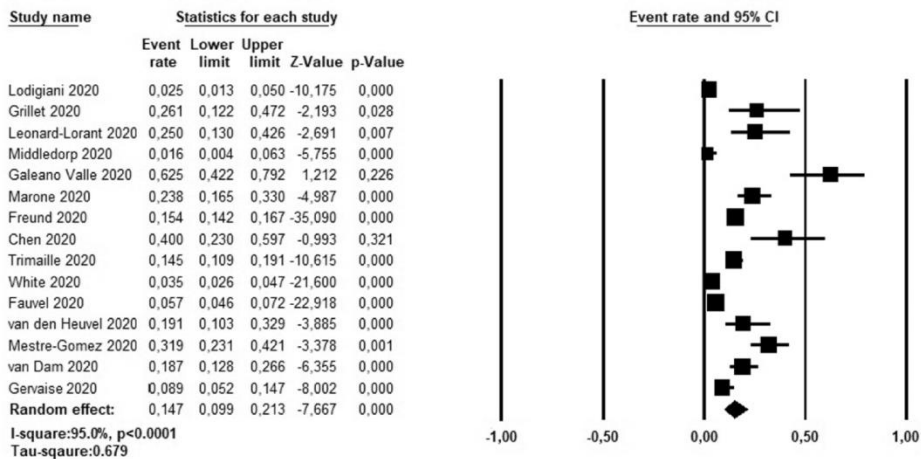
Secondary endpoints.

	Control N = 30	Nintedanib N = 30	P Value
Ventilator-free days within 28 days	12 (0–17)	17 (0–21)	0.038
Percentage of high-attenuation areas on CT			
Induction of mechanical ventilation (%)	29.1 (20.3–33.1)	30.8 (20.9–46.7)	0.651
Liberation from mechanical ventilation (%)	38.7 (20.9–45.6)	25.7 (9.4–34.6)	0.027
Gastrointestinal adverse events			
Mild events	27 (90%)	25 (83.3%)	0.448
Moderate events	6 (20%)	9 (30%)	0.371
Severe events	3 (10%)	2 (6.7%)	0.640
Acute liver failure			
Mild	20 (66.7%)	24 (80%)	0.243
Moderate	6 (20%)	11 (36.7%)	0.158
Severe	2 (6.7%)	2 (6.7%)	1.00

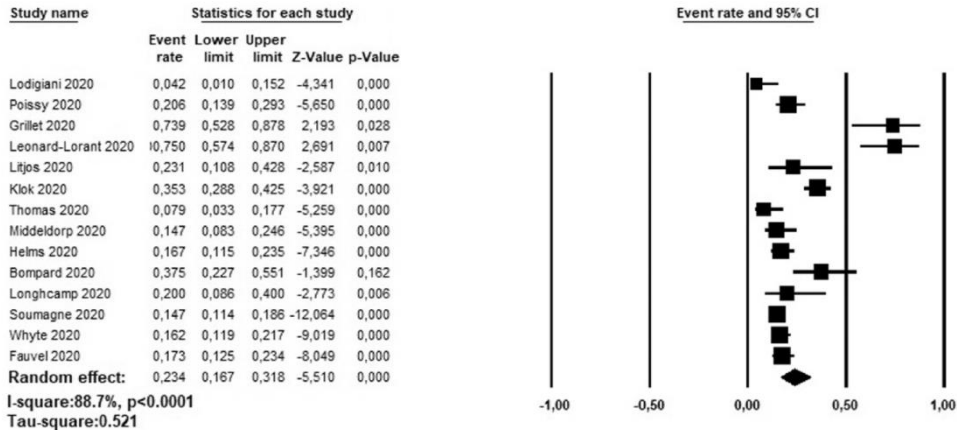
CT, computed tomography.

Pulmonary Embolism

A - General Wards



B - ICU



- The cumulative in-hospital rate of acute PE in COVID-19 patients hospitalized in general wards : 1.6 ~ 62.5%
- Pooled incidence of acute PE : 14.7% (95% CI: 9.9–21.3%, I²=95.0%)

- The cumulative in-hospital rate of acute PE in COVID-19 patients hospitalized in ICU: 4.2~75.0%
- Pooled incidence of acute PE : 23.4% (95% CI: 16.7–31.8%, I²=88.7%)

Pulmonary Embolism

US, March 16, 2020, to April 18, 2020,
COVID19 with Acute PTE (N=72,22%) VS COVID19 without Acute PTE (N=256,78%)

Table 1: Multivariable Model Demonstrating Odds Ratios of Statistically Significant Variables with Confidence Intervals

Variable	Odds Ratio	P Value
BMI >30 kg/m ²	2.7 (1.3, 5.5)	.006
D-dimer value*	4.8 (3.2, 7.2)	.001
Statin therapy	0.4 (0.2, 0.8)	.005
History of PE	3.5 (1.2, 10.5)	.02
Hypertension	0.5 (0.2, 1.0)	.04

Note.—Data in parentheses are 95% confidence intervals. Nonsignificant variables considered for inclusion included age, sex, race, previous history of cancer, previous surgery within 4 weeks, a prior pulmonary embolism (PE), smoking history, presence of diabetes, chronic obstructive pulmonary disease, congestive heart failure, oxygen requirements, ferritin, lactate dehydrogenase, C-reactive protein level, and platelets. BMI = body mass index.

* Increase by 6 µg/mL.

Pulmonary Embolism

Italy, Retrospective multicenter study, 7 Italian Hospitals, PE: 32 cases (14%)

Table 3
Univariable and multivariable regression analyses for the occurrence of pulmonary embolism.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Pulmonary embolism				
TAPSE, mm	0.78 (0.73–0.88)	<0.001	0.84 (0.66–0.98)	0.046
sPAP, mmHg	1.08 (1.04–1.12)	<0.001	1.12 (1.03–1.23)	0.008
Time between hospitalization and symptoms onset, days	1.07 (1.03–1.11)	0.001	–	–
D-dimer, value ^a	1.02 (1.006–1.045)	0.010	–	–
Acute cardiac injury	2.25 (1.05–4.83)	0.037	–	–

CI, confidence interval; OR, odds ratio; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

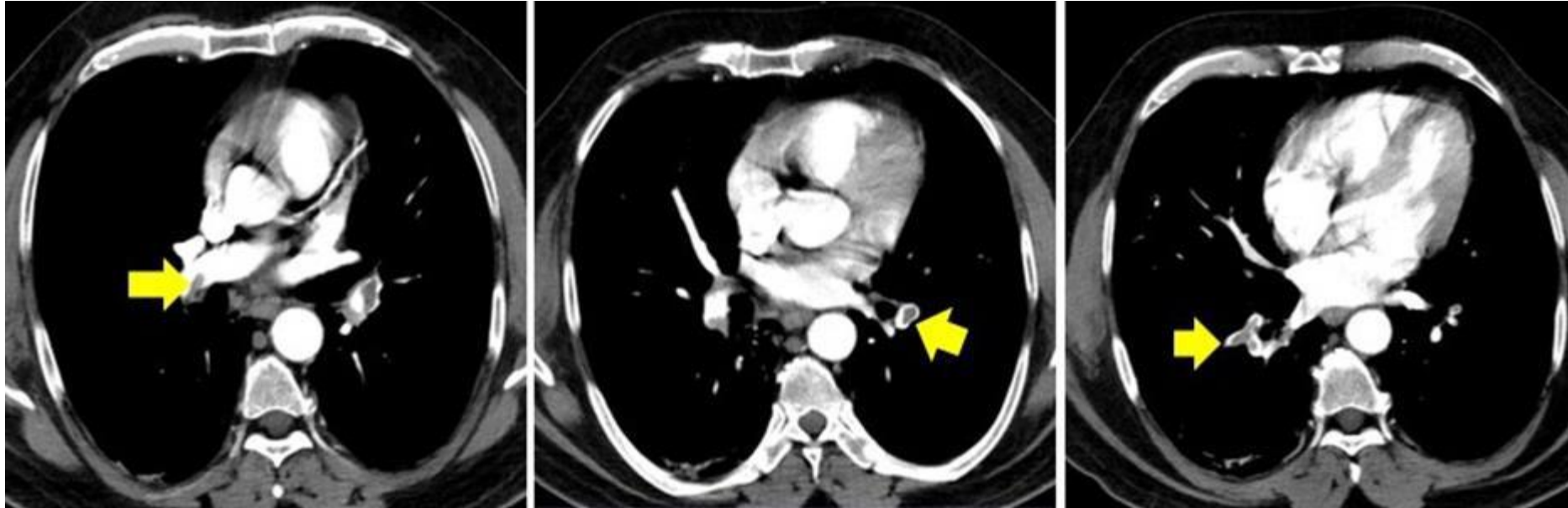
^a Odds ratio reflects risk with increases of 0.01.

Table 4
In-hospital adverse events in the enrolled patients.

	Total (n = 224)	Pulmonary embolism (n = 32)	No pulmonary embolism (n = 192)	p-Value
Mortality	68 (30)	16 (50)	52 (27)	0.010
Cardiogenic shock	39 (17)	12 (37)	27 (14)	0.001
ARDS	107 (48)	20 (62)	87 (45)	0.072
IMV	68 (30)	13 (41)	55 (29)	0.172
NIV	100 (45)	16 (50)	84 (44)	0.510

ARDS, acute respiratory distress syndrome; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation.

Pulmonary Embolism



After the acute phase of the disease, the state of hyper-coagulation may last for a long time, so long-term prophylaxis may be recommended in cases with severe disease => *not clear yet.*

Pulmonary Embolism

- In cases with severe disease and accompanying pulmonary embolism, anticoagulation administration is required according to the recommendations by the specific guidelines.
- Evaluate the patient for the development of pulmonary hypertension at the end of 12 weeks, and discontinue the treatment at the end of the 3rd month if PHT has not developed.
- Measurement and follow-up of D-Dimer level, which is also an acute phase reactant and is not specific for COVID-19, for chronic embolism is controversial.

Anticoagulant Treatment for Thrombosis

- The Panel recommends that when diagnostic imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease be managed with therapeutic anticoagulation **(AIII)**.
- The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Pneumothorax

Table 1
Summary and characteristics of nine observational studies for COVID-19 patients with pneumothoraces.

Author	Study design	Study type	Month, year	Country	Patients (N)	Patient type	Incidence PTX (%)	Age (Y) Mean +/- SD, Median (IQR)	Male, N (%)
<i>COVID-19 Observational Studies</i>									
Cates et al. ¹⁷	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	October 2020	USA	3948	Hospitalized, Adults	0.6	70.0 (61–77)	3710 (94)
Ding et al. ²	Retrospective Cohort, Single-center	Radiologic Characteristics COVID-19	April 2020	China	112	Hospitalized, Adults/Children	3.6	55.8 +/- 16.1	51 (45.5)
Ekanem et al. ¹⁵	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	January 2021	USA	1619	Hospitalized, Adults	1.4	60.0 (47.0–67.0)*	18 (81.2)*
Guo et al. ¹⁸	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	May 2020	China	105	Hospitalized, Adults	1.0	67.0 (64–74)	48 (45.7)
Martinelli et al. ¹⁶	Retrospective Cohort, Multi-center	Clinical Characteristics COVID-19	November 2020	UK	71	Hospitalized, Adults	84.5	NR	48 (77.4)*
McGuinness et al. ¹³	Case-Control, Single-center	Radiologic Characteristics COVID-19	June 2020	USA	601	ICU, Adults	12.8	63.0 +/- 2.0	426 (70.9)
Miro et al. ¹⁴	Case-Control, Multi-center	Clinical Characteristics COVID-19	January 2021	Spain	71,904	Hospitalized, Adults	0.06	66 (47–74)*	29 (72.5)*
Wang et al. ¹⁹	Cross-Sectional, Single-center	Clinical Characteristics COVID-19	October 2020	China	248	Hospitalized, Adults	2.0	64.2 +/- 9.1*	5 (100)*
Zantah et al. ²⁰	Cross-Sectional, Single-center	Clinical Characteristics COVID-19	September 2020	USA	902	Hospitalized, Adults	0.6	59.5 +/- 14.2*	2 (33.3)*
Author	Location* (%)	Chest Tube* (%)	Pneumomediastinum (%)	Time to PTX (D) Mean +/- SD, Median (IQR)	Lung Disease (%)	Smoking Status (%)	IMV (%)	Mortality (%)	ECMO* (%)
<i>COVID-19 Observational Studies</i>									
Cates et al. ¹⁷	NR	NR	NR	NR	Asthma/ COPD (30.8)	NR	NR	21.0	NR
Ding et al. ²	NR	NR	NR	10 <	NR	NR	NR	NR	NR
Ekanem et al. ¹⁵	NR	72.7	NR	9.0 (4.0 - 15.0)	Asthma/ COPD (18.2)	13.6*	40.9*	36.4*	9.1
Guo et al. ¹⁸	NR	NR	NR	NR	Unspecified (8.6)	12.4	7.6	2.9	NR
Martinelli et al. ¹⁶	NR	51.6	9.7*	NR	Asthma/ Bronchiectasis/ COPD (30)*	29.0*	45.0*	88.3*	20.0
McGuinness et al. ¹³	Right (45.5), Left (40.2), Bilateral (14.3)	NR	10	5.4 (0–41) [IMV]	NR	33.7*	100*	57.0	NR
Miro et al. ¹⁴	Right (81.1), Left (18.9)	72.5	16.2*	NR	Asthma/ COPD (30)	10.0*	NR	NR	NR
Wang et al. ¹⁹	Right (60), Bilateral (40)	60.0	20*	19.6 +/- 10.2	NR	NR	100*	80.0*	20
Zantah et al. ²⁰	Bilateral (50), Left (33.3), Right (16.7)	100	NR	11 +/- 5.9	ILD (16.7)*	NR	66.7	66.7*	16.7

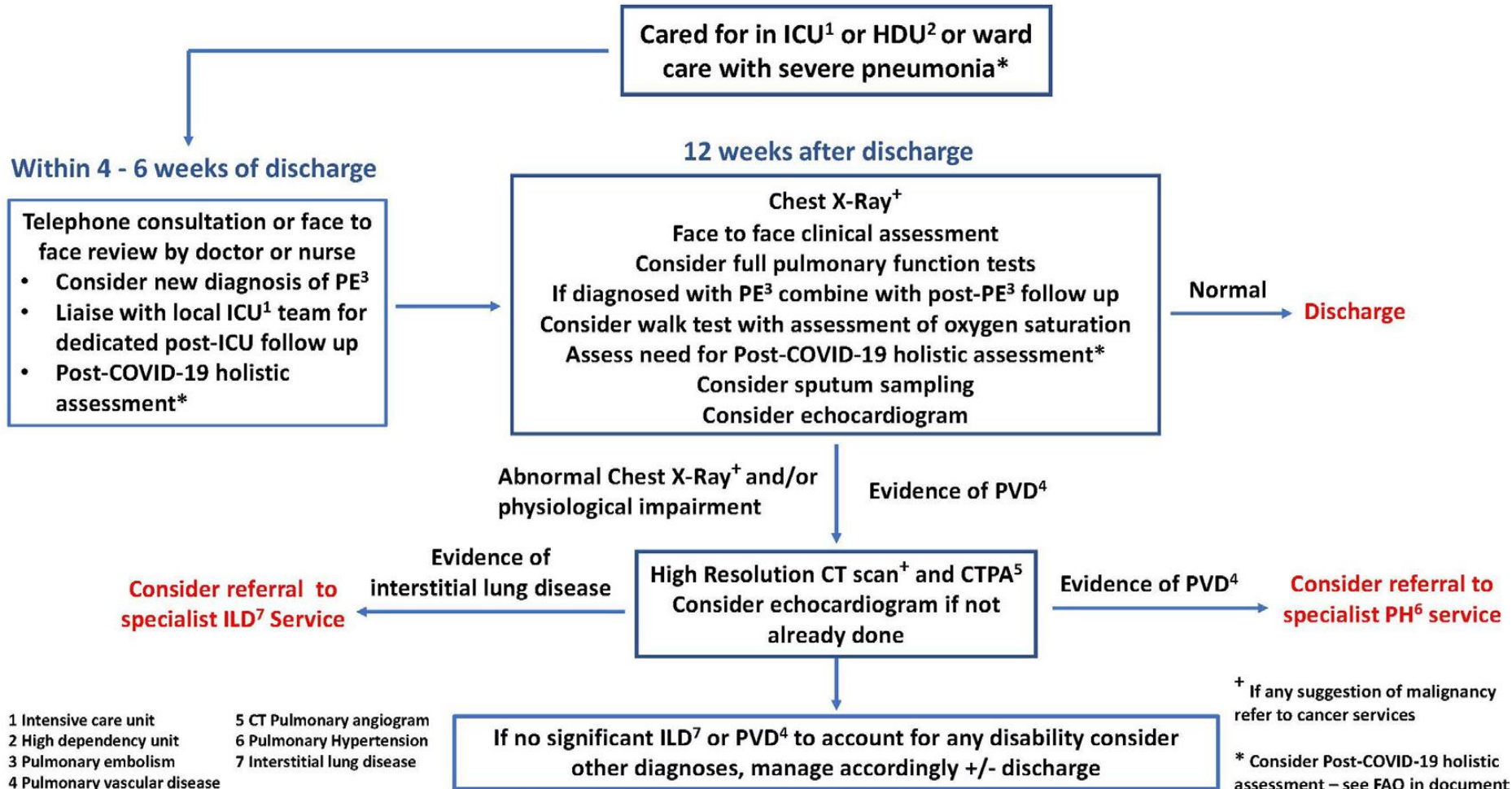
* Among COVID-19 patients who develop pneumothoraces.

Abbreviations: COPD: chronic obstructive pulmonary disease, ECMO: extracorporeal membrane oxygenation, ICU: intensive care unit, ILD: interstitial lung disease, IMV: invasive mechanical ventilation, IQR: interquartile range, N: number of patients, NR: non-reported, PTX: pneumothorax, SD: standard deviations, Y: years.

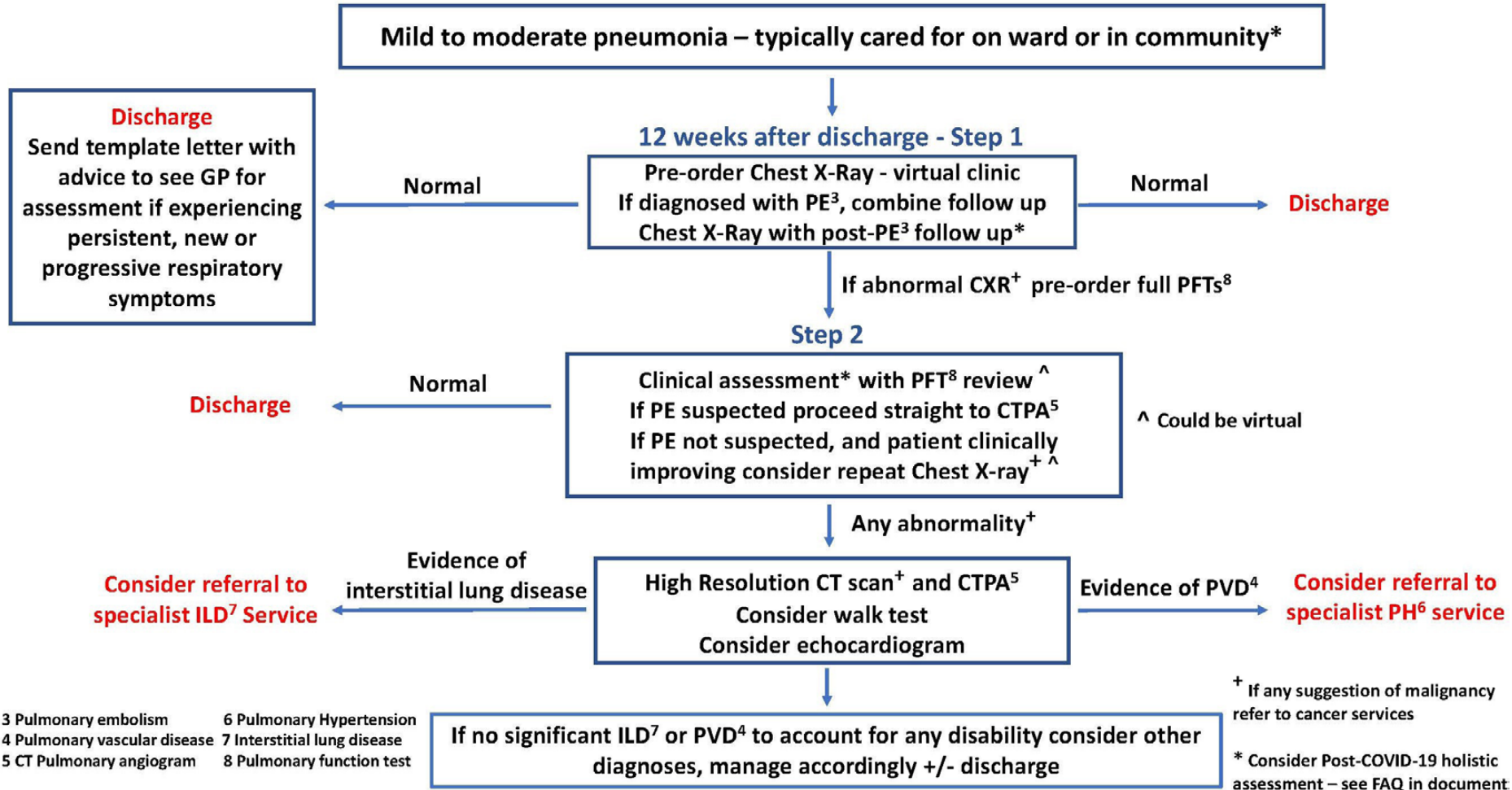
Pneumothorax

- Incidence : low at 0.3% in hospitalized COVID-19 patients
 - Increases to 12.8-23.8% in those requiring invasive MV (a high mortality rate up to 100%)
- The time to diagnosis: around 9.0-19.6 days from admission
 - 5.4 days after invasive MV initiation
- Associated with prolonged hospitalization, increased likelihood of ICU admission and death, especially among the elderly
- Tends to be unilateral and right-sided
- Age, pre-existing lung diseases, and active smoking status are not shown to be risk factors

Management



Management



Other Complications

Hematologic

- Thromboembolic events have been noted to be <5% in post-acute COVID-19 in retrospective studies
- The duration of the hyperinflammatory state induced by infection with SARS-CoV-2 is unknown
- Direct oral anticoagulants and low-molecular-weight heparin may be considered for extended thromboprophylaxis after risk-benefit discussion in patients with predisposing risk factors for immobility, persistently elevated D-dimer levels (greater than twice the upper limit of normal) and other high-risk comorbidities such as cancer

Cardiovascular

- Persistent symptoms may include palpitations, dyspnea and chest pain
- Long-term sequelae may include increased cardiometabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI), arrhythmias, tachycardia and autonomic dysfunction
- Patients with cardiovascular complications during acute infection or those experiencing persistent cardiac symptoms may be monitored with serial clinical, echocardiogram and electrocardiogram follow-up

Neuropsychiatric

- Persistent abnormalities may include fatigue, myalgia, headache, dysautonomia and cognitive impairment (brain fog)
- Anxiety, depression, sleep disturbances and PTSD have been reported in 30–40% of COVID-19 survivors, similar to survivors of other pathogenic coronaviruses
- The pathophysiology of neuropsychiatric complications is mechanistically diverse and entails immune dysregulation,

inflammation, microvascular thrombosis, iatrogenic effects of medications and psychosocial impacts of infection

Renal

- Resolution of AKI during acute COVID-19 occurs in the majority of patients; however, reduced eGFR has been reported at 6 months follow-up
- COVAN may be the predominant pattern of renal injury in individuals of African descent
- COVID-19 survivors with persistent impaired renal function may benefit from early and close follow-up in AKI survivor clinics

Endocrine

- Endocrine sequelae may include new or worsening control of existing diabetes mellitus, subacute thyroiditis and bone demineralization
- Patients with newly diagnosed diabetes in the absence of traditional risk factors for type 2 diabetes, suspected hypothalamic-pituitary-adrenal axis suppression or hyperthyroidism should undergo the appropriate laboratory testing and should be referred to endocrinology

Gastrointestinal and hepatobiliary

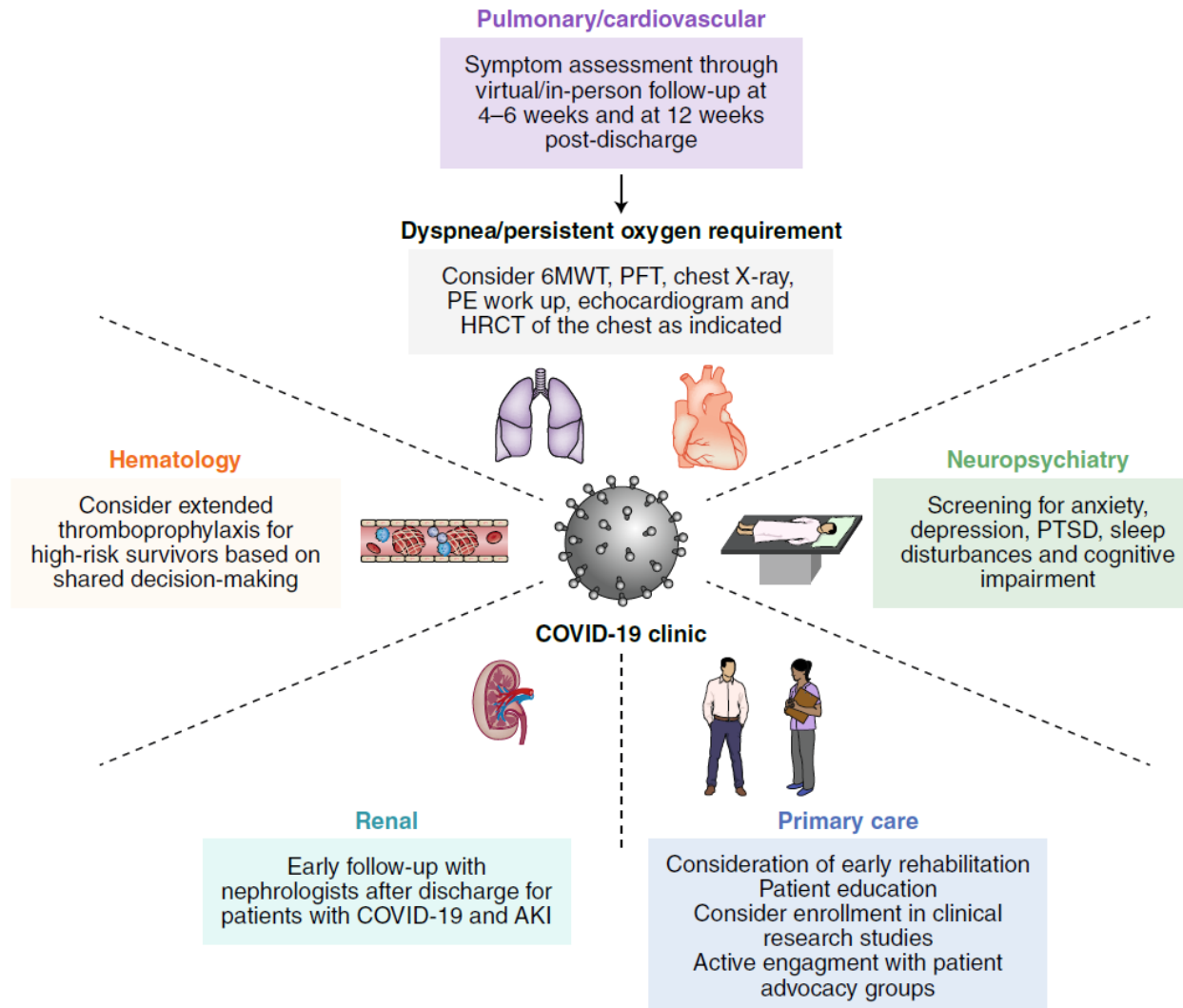
- Prolonged viral fecal shedding can occur in COVID-19 even after negative nasopharyngeal swab testing
- COVID-19 has the potential to alter the gut microbiome, including enrichment of opportunistic organisms and depletion of beneficial commensals

Dermatologic

- Hair loss is the predominant symptom and has been reported in approximately 20% of COVID-19 survivors



Interdisciplinary Management



Take-home Messages

- Lung fibrosis:
 - Prevalence: 35~75%
 - Risk factors: MV care, HTN, Age, Higher IL-6, CRP, D-dimer, lower lymphocyte, IFN-r, albumin
 - Prognosis: Still much uncertainty
 - Promising Tx: Antivirals, Anti-inflammatory drugs(steroids), Antifibrotics + rehabilitation, supportive care
- Pulmonary embolism:
 - Pooled incidence of acute PE : Ward 14.7%, ICU 23.4%
 - Risk factors: BMI >30kg/m², D-dimer >6ug/ml, History of PE, increased sPAP
 - Tx: Therapeutic anticoagulation
- Pneumothorax:
 - Incidence: low at 0.3% in hospitalized COVID-19 pts, 12.8-23.8% in MV
 - Prolonged hospitalization, increased likelihood of ICU admission and death

“Thank you for your attention.”