Post COVID-19 Fibrosis Pulmonary Rehabilitation

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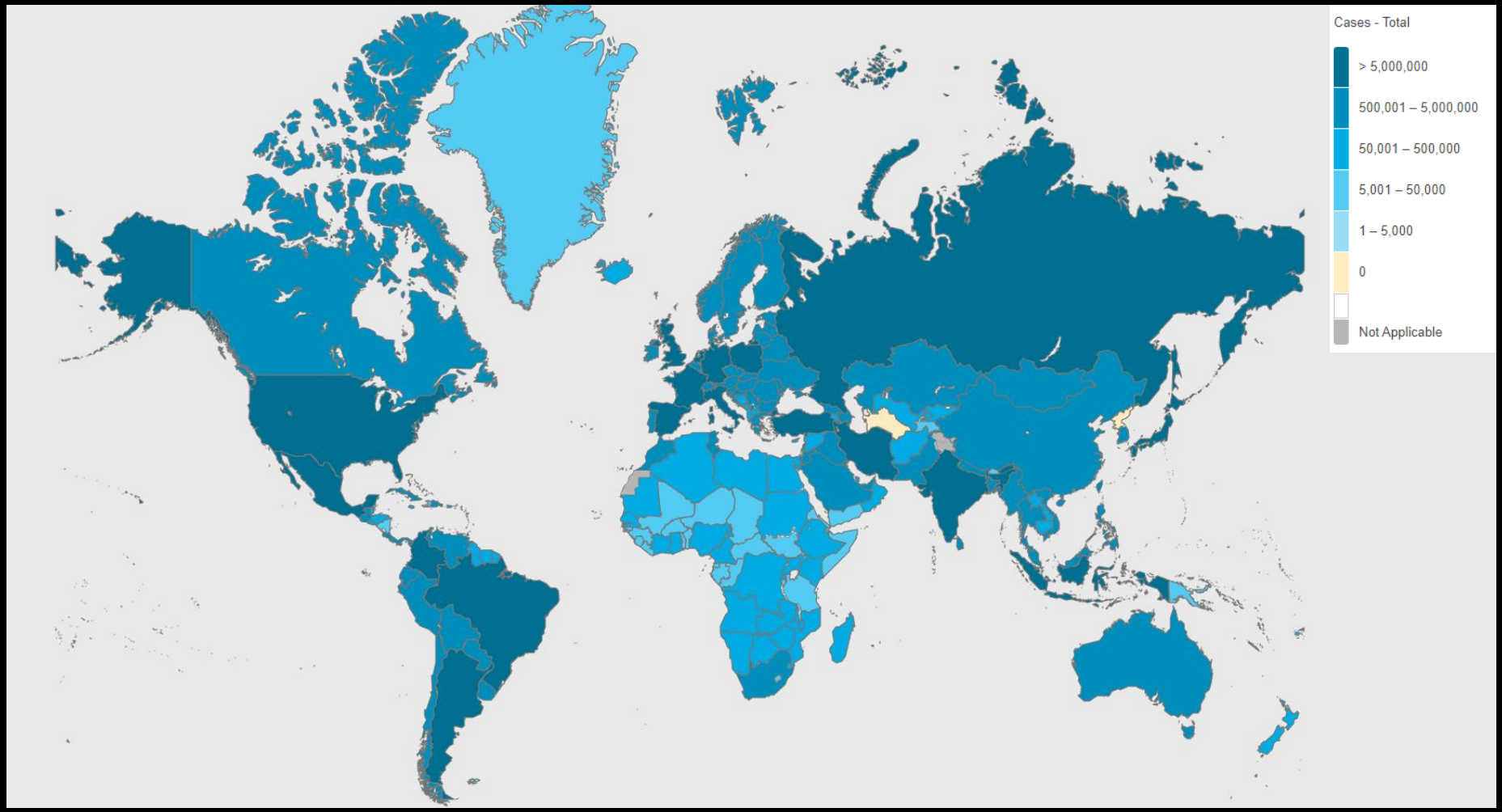
Introduction

Coronavirus disease (COVID-19) pandemic

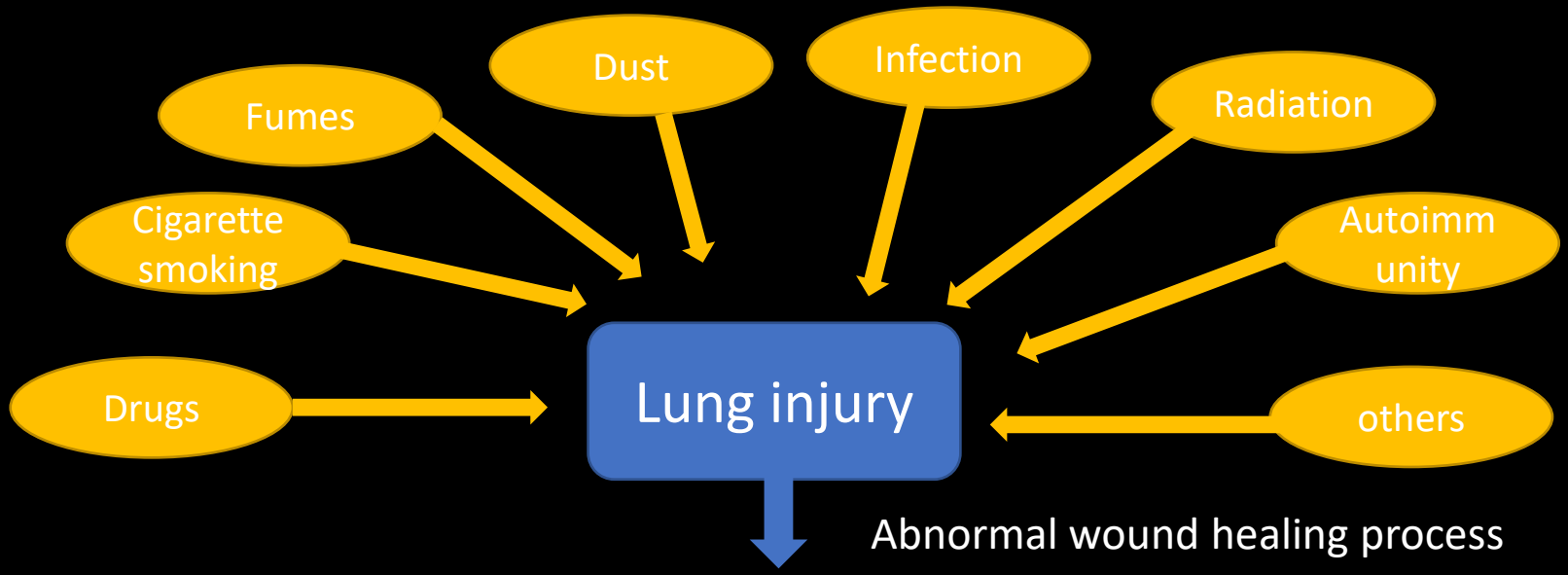


Post COVID-19 condition (long COVID)

https://www.who.int/

Pulmonary fibrosis

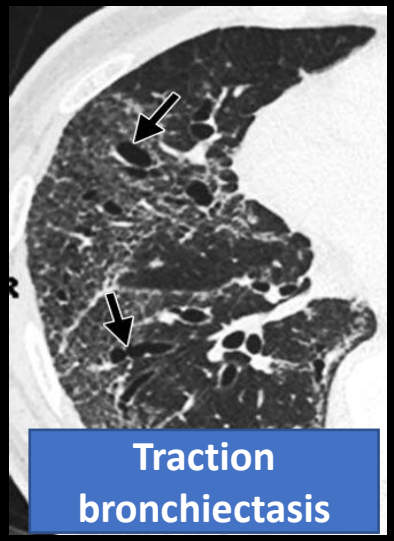
- Pulmonary fibrosis = scarring in the lungs



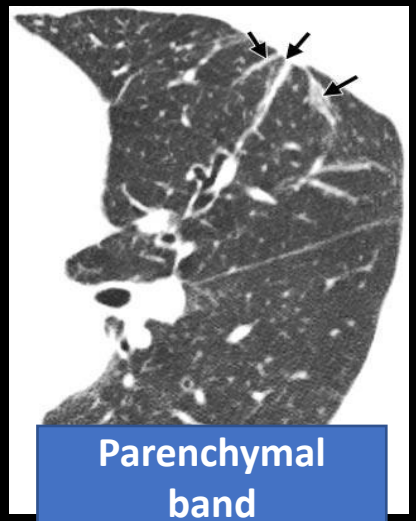
Progressive pulmonary fibrosis	
• Silicosis/Sarcoidosis • Coal workers pneumonoconiosis • Ankylosing spondylitis • Radiation	• Idiopathic pulmonary fibrosis • Systemic sclerosis • Asbestosis • Rheumatoid arthritis

CT finding in Pulmonary fibrosis

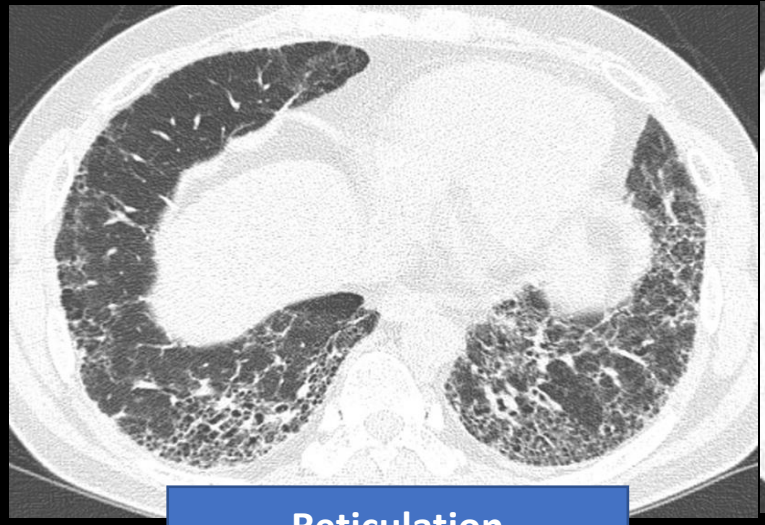
Architectural distortion



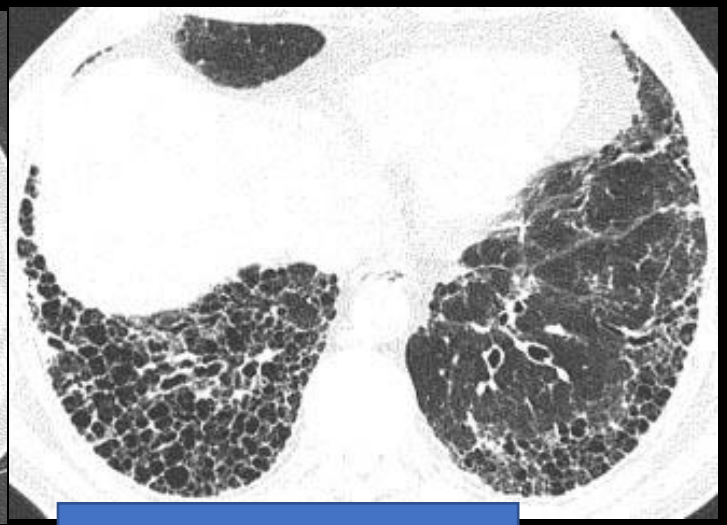
Traction bronchiectasis



Parenchymal band



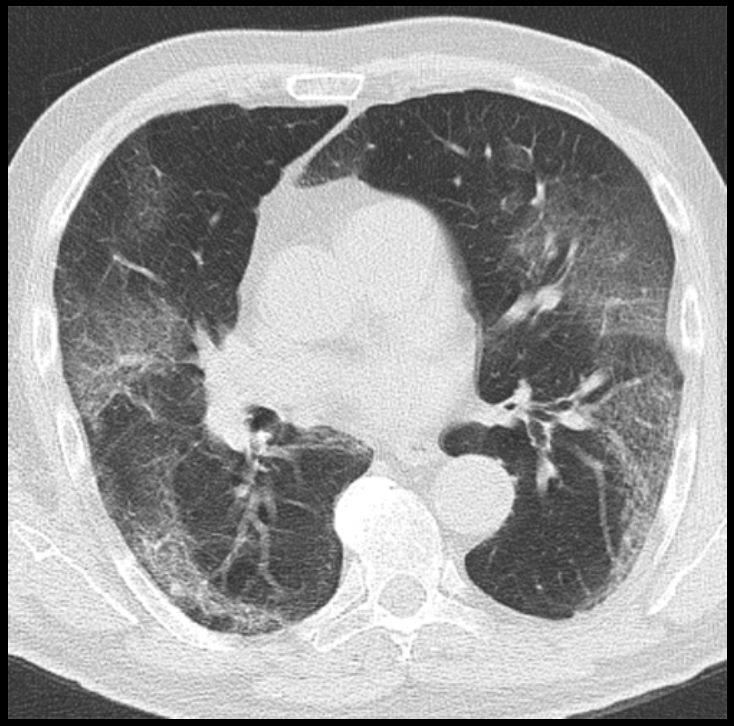
Reticulation



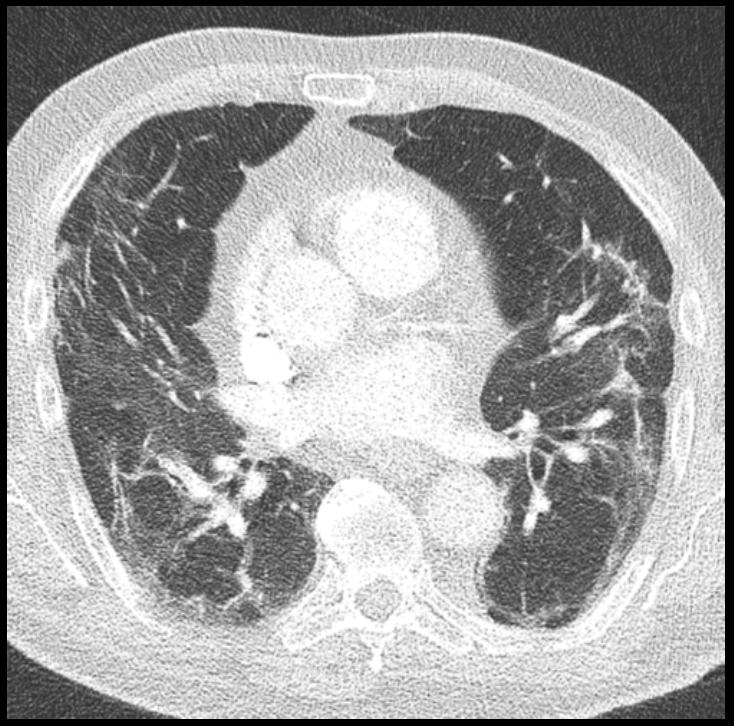
Honeycombing

Radiology. 2008 Mar;246(3):697-722.

Follow-up in COVID-19 Pneumonia



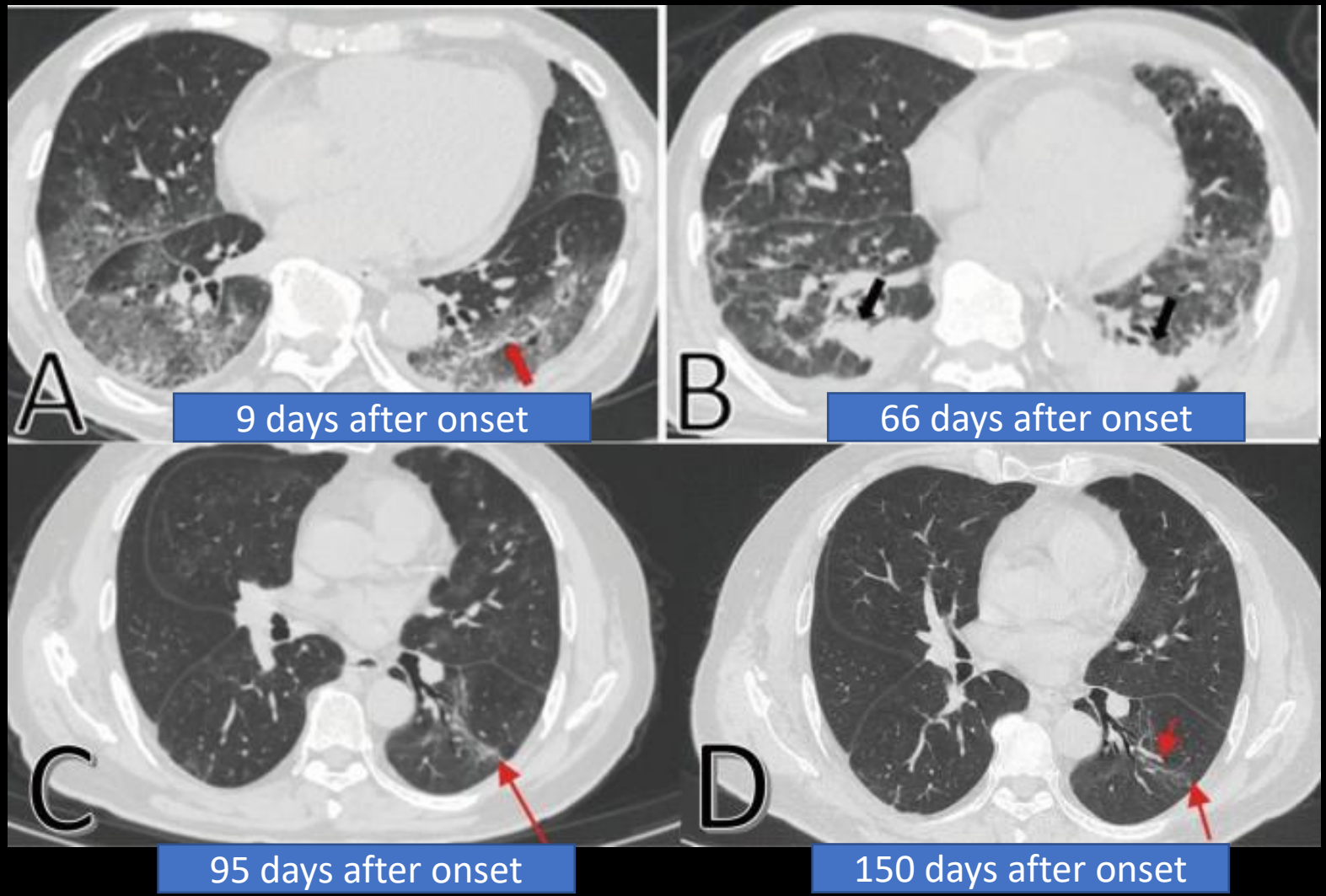
onset



8 weeks later

Radiographics. 2020 Nov; 40(7): 1848–1865.

Follow-up in COVID-19 Pneumonia



Respir Res . 2021 Jul 9;22(1):203.

Post-COVID-19 pulmonary fibrosis

When and how can we define Post COVID-19 fibrosis?

Epidemiology & Risk factor

Incidence

	Subject	definition	Follow-up	incidence
Han et al. 2021	Prospective, n=114명 NIV: 24 (21%) MV: 4 (3.5%)	traction bronchiectasis parenchymal bands ± honeycomb	6 month after Diagnosis	35%
Caruso et al. 2021	Prospective, n= 118 NIV: 53 (61%) MV: 34 (39%)	reticular pattern ± honeycombing	6 month after Diagnosis	72%
Gassel et al. 2021	Retrospective, n=48 MV: 48 (100%)	coarse fibrous bands ± obvious parenchymal distortion bronchiectasis/nbronchiolectasis	3 month after discharge	67%
Gulati et al. 2021				0%
COMEBAC Study Group 2021	MV: 51 (28.8%)	NA	discharge	19%
Huanng et al, 2021	Prospective, n=81 NIV: 21 (25.9%) MV: 14 (17.3%) ICU: 45 (55.6%)	parenchymal bands, irregular interfaces reticular opacities traction bronchiectasis ± honeycombing	Median 58 after discharge	52%
Nabahati et al 2021	Prospective, n=173	traction bronchiectasis, honeycombing, parenchymal bands, interlobar septal thickening	3month after discharge	52%

The incidence of post COVID-19 fibrosis has been reported to vary from 20 to 70%, depending on the **severity of the disease**, the **definition of fibrosis** and the **follow-up duration of the study**

Risk factors for pulmonary fibrosis after COVID-19

	Risk factors
Demographics	• Gender • Old age • Body mass index • Comorbidities (diabetes, obesity, hypertension, chronic lung diseases, chronic liver disease, cardiovascular diseases and cerebrovascular disease) • Length of telomere • Smoking/Alcohol abuse
Disease related factors	• Use of high flow oxygen or invasive or non-invasive ventilation • Long duration of hospital or ICU stay • Unstable initial vital sign (tachycardia, high fever, tachypnea) • Presence of ARDS • Absence of cough as an initial presentation • Persistent dyspnea
Laboratory factors	• Increased in IL-6, WBC, neutrophil, eosinophil, NLR, total bilirubin, CRP, LDH, d-dimer, BNP, procalcitonin • Decreased in lymphocyte, albumin
Radiological factors	• Extent of abnormal lesion in initial chest CT • The presence of consolidation, reticulation, parenchymal band, interstitial thickening, irregular interface, pleural effusion, and poor-aerated lung volume

Respir Res . 2021 Jul 9;22(1):203.

Risk factors for Post-COVID 19 pulmonary fibrosis

- 90 days follow-up, n=288 (mechanical ventilator=3.1%)

A

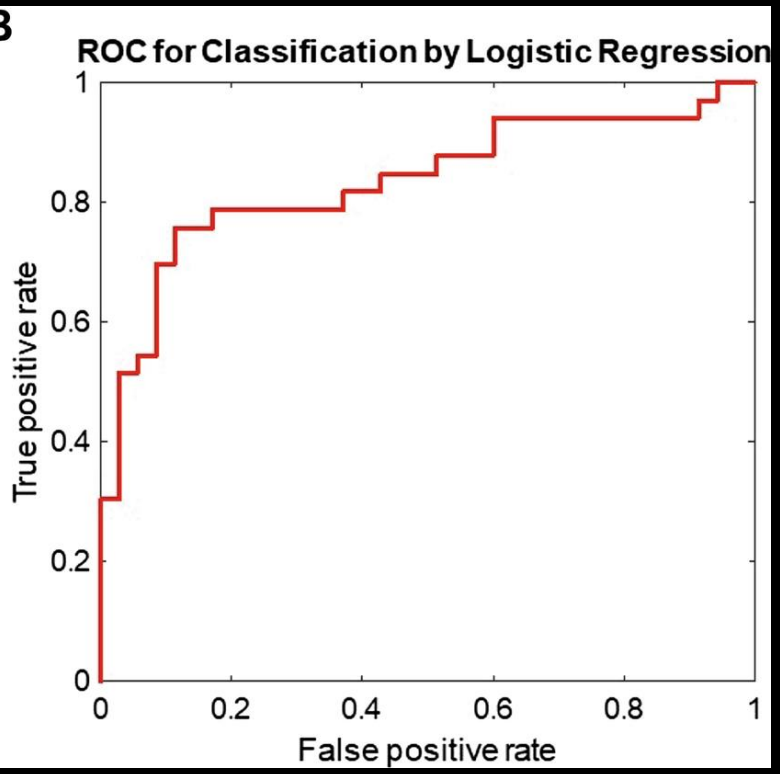
Parameters	*P*
Age	<0.00001
BMI	<0.034
Fever	0.055
Highest PCT	<0.002

C

fibrosis

		Predicted	
		GA	GB
Actual	GA	77	38
	GB	31	142

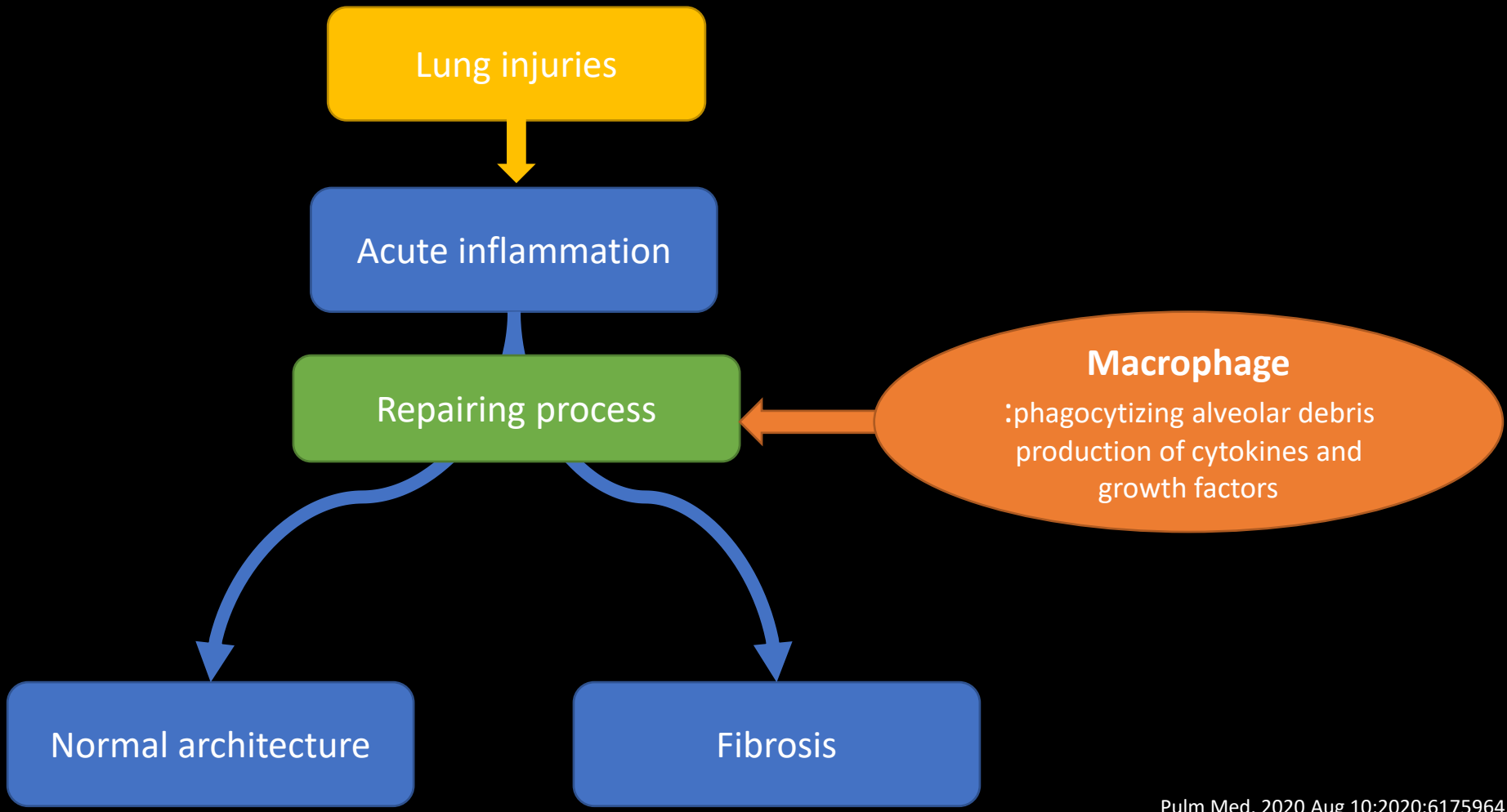
B



AUC	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
0.84	67%	82%	76%	71%	79%

Pathogenesis

Pathogenesis of fibrosis



Pulm Med. 2020 Aug 10;2020:6175964.

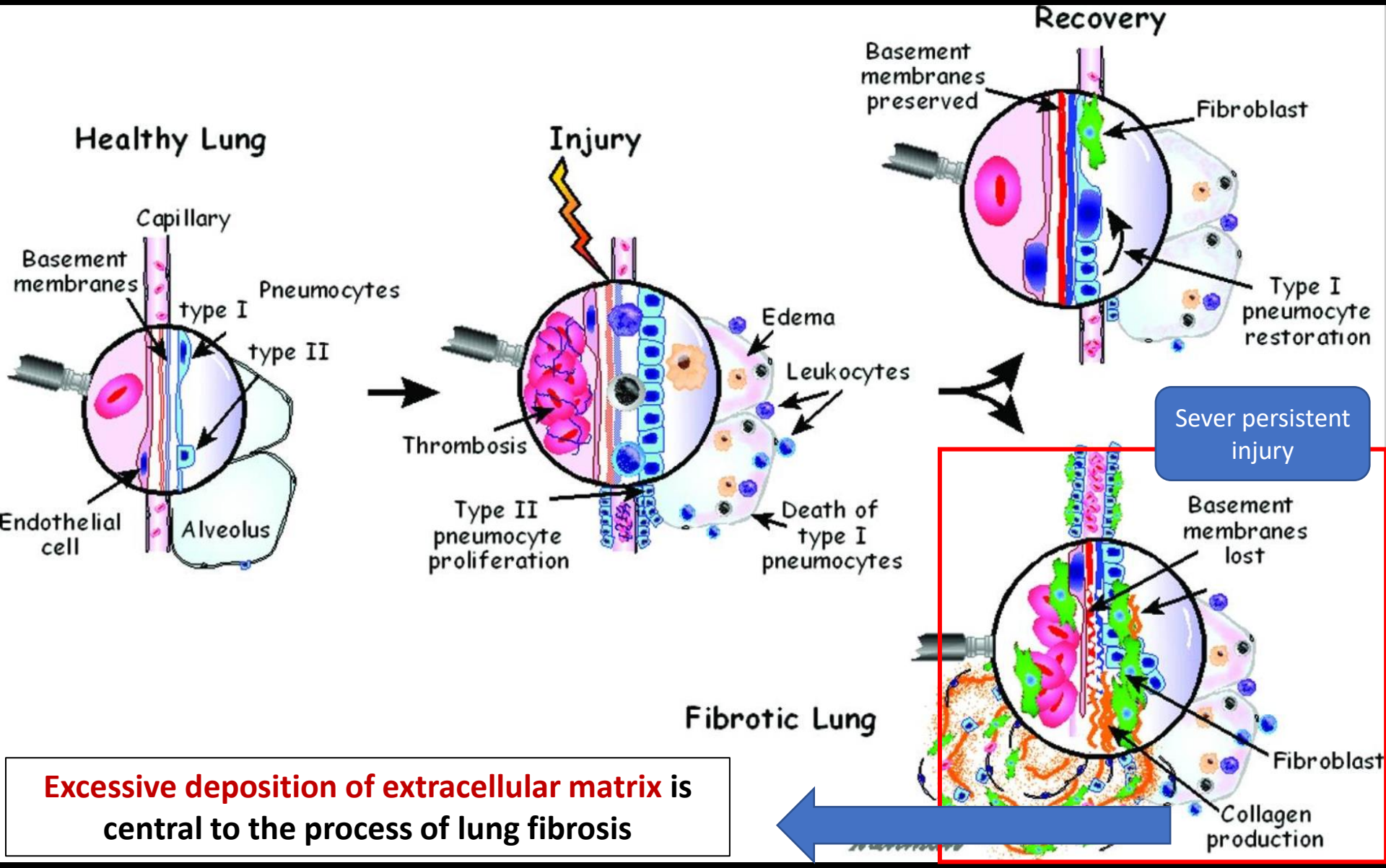
Pathogenesis of fibrosis

- **Repairing process**: angiogenesis, fibroblast activation, collagen deposition
- Organization: fibroblastic invasion of the alveoli and transformation into myofibroblasts leading to the deposition of an organizing fibroblastic extracellular matrix (ECM)

EGF, TGF-α	VEGF, FGF
proliferation of bronchiolar stem cells to replace damaged alveolar epithelium	migration and proliferation of uninjured endothelial cells leading to pulmonary capillary angiogenesis

EGF, Epidermal growth factor; TGF-α: transforming growth factor-alpha ,VEGF: Vascular endothelial growth factor (VEGF); FGF, fibroblast growth factor

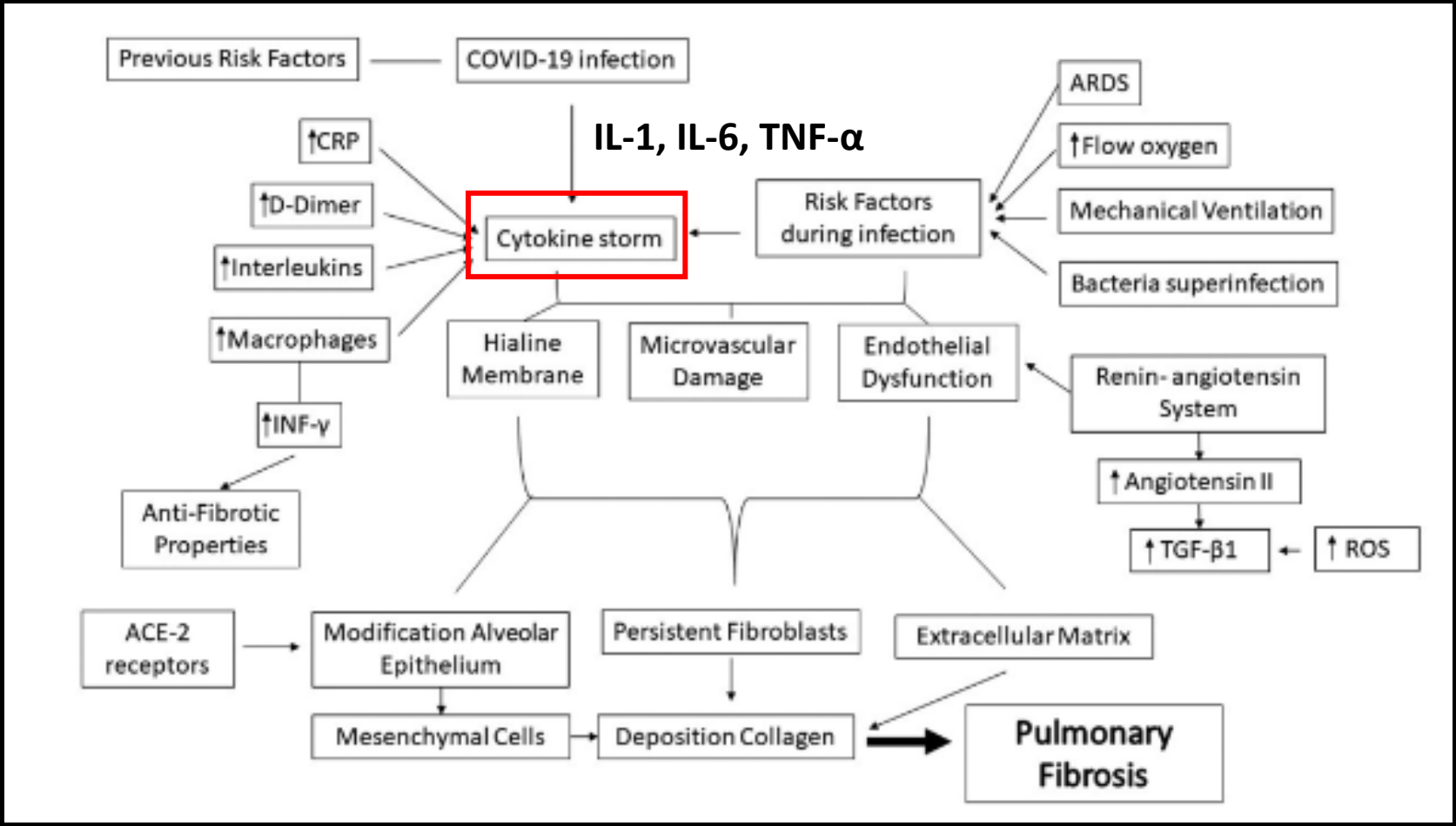
Pulm Med. 2020 Aug 10;2020:6175964.



Excessive deposition of extracellular matrix is central to the process of lung fibrosis

Chest. 2009 Nov; 136(5): 1364–1370.

Pathogenesis of fibrosis in COVID-19

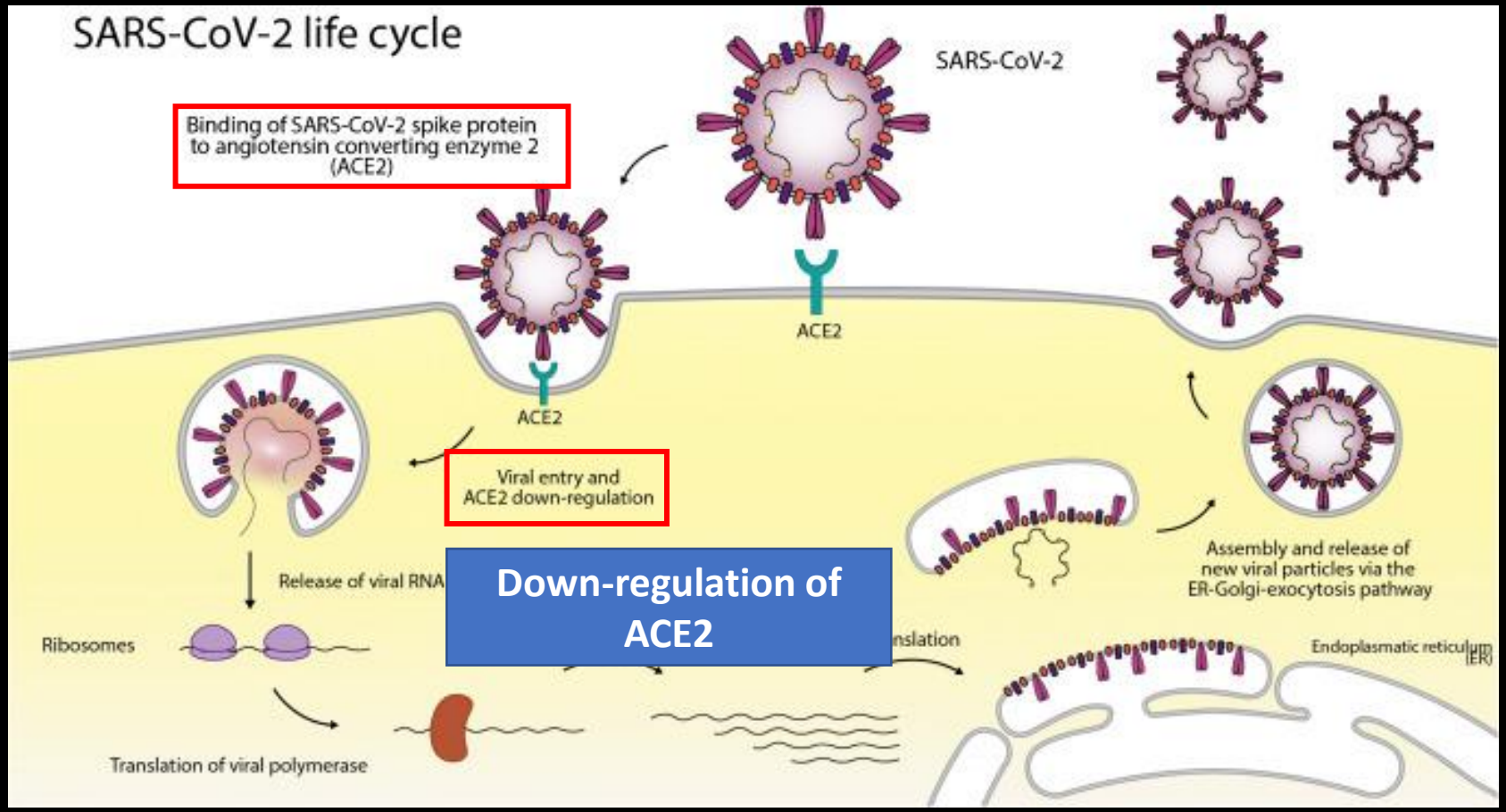


EXPERT REVIEW OF RESPIRATORY MEDICINE
2021, VOL. 15, NO. 6, 791–803

Pathogenesis of fibrosis in COVID-19

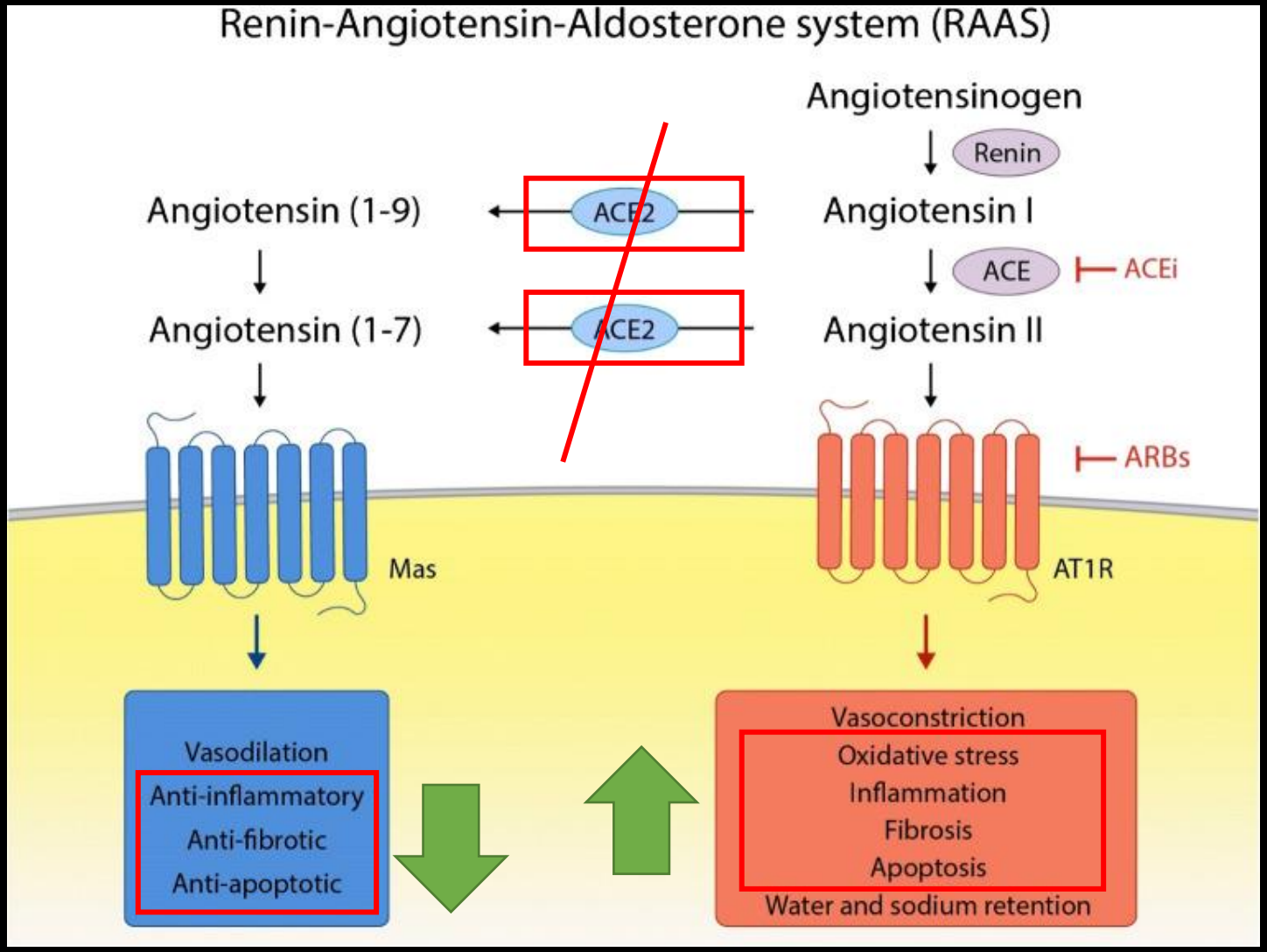
- **Tumor necrosis factor-alpha (TNF-α)**
- induces loss of expression of fibroblast Thy-1 surface, leading to myofibroblast differentiation.
- increased expression in IPF lung
- anti–TNF-α antibody diminish pulmonary fibrosis in both bleomycin-induced and silica-induced pulmonary fibrosis in mice model
- **Interleukin-6 (IL-6)**
- stimulate profibrotic pathway in fibroblast from IPF, while it enhance apoptosis pathway in normal fibroblast.
- Circulating IL-6 las was significantly increased in bleomycin-induced pulmonary fibrosis mice than that in control mice
- pathway mediated by soluble IL-6R α activates proliferation of fibroblast and production of ECM

Pathogenesis of fibrosis in COVID-19



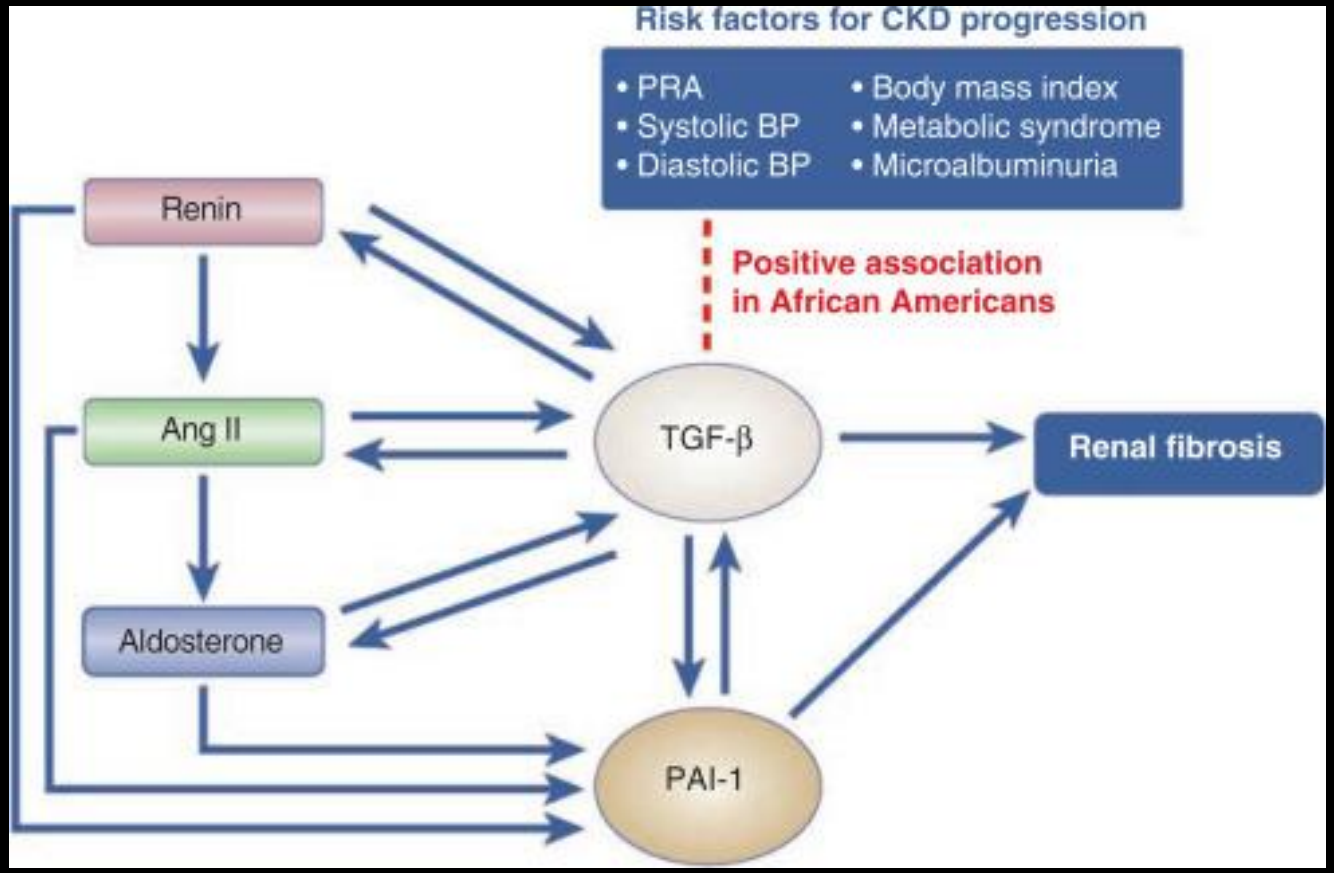
Eur J Clin Microbiol Infect Dis. 2021; 40(5): 905–919.

Pathogenesis of fibrosis in COVID-19



Eur J Clin Microbiol Infect Dis. 2021; 40(5): 905–919.

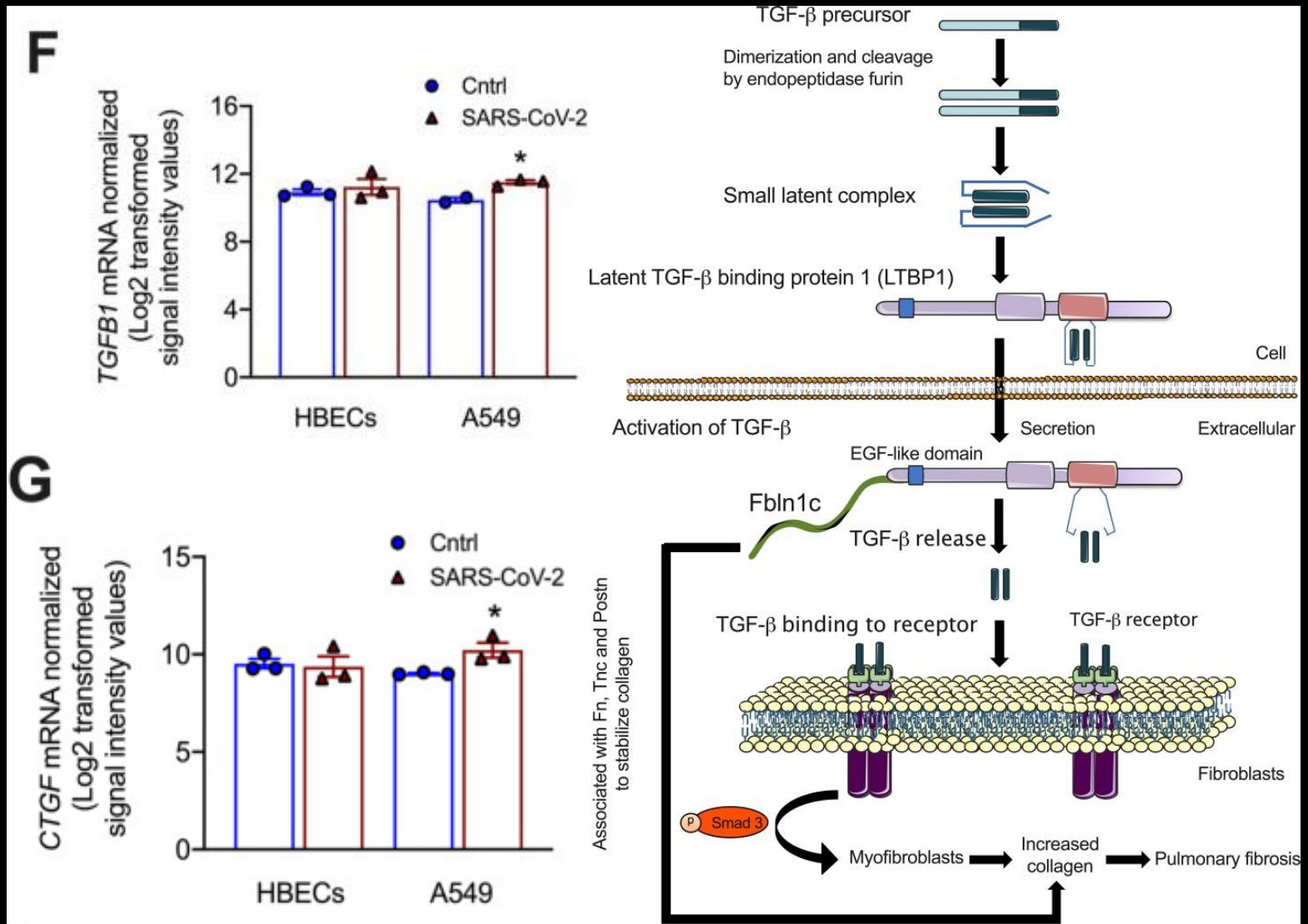
Pathogenesis of fibrosis in COVID-19



Diabetes Res Clin Pract. 2017 Nov;133:124-130

Respir Res. 2020; 21: 182.
JCI Insight. 2019 Aug 22; 4(16): e124529.

Pathogenesis of fibrosis in COVID-19



Pathogenesis of fibrosis in COVID-19

- **Oxidative stress**
- ARDS, High flow nasal canula, long oxygen supply → risk factor for fibrosis.
- Hyperoxia induces reactive oxygen species generation in mitochondria, with inhibition of oxidative phosphorylation and reduction of adenosine triphosphate level → similar to the pathogenesis of IPF in mitochondria.
- In a 4-month follow-up USA study (n=76), 10% decrease in age-adjusted telomere length increases 35% development of fibrotic-like pattern (95% CI: 1.06-1.72)
- Telomere shortening or mutation is associated with development of IPF.

Clinical manifestations & Radiological/histopathological findings

Clinical manifestations

- Variable degrees of clinical symptoms including dyspnea, dry cough, fatigue
- Lung auscultations: normal ~ patchy, diffuse crackles
- Normal oxygen saturation ~ needed for oxygen supplies

➔Oxygen demand was mostly reduced during follow-up

- Pulmonary function test & Exercise test

Lung Function	Exercise
DLCO ↓↓	Reduced performance
TLC ↓	VO2 ↓
FEV1 ↓ ↔	6MWD ↓
FVC ↓ ↔	

DLCO: diffusion capacity for carbon monoxide, FVC: forced vital capacity, FEV1: forced expiratory volume in the first second, TLC: total lung capacity, VO2: peak oxygen uptake, 6MWD: 6-minute walk distance

Clinical manifestations

- 3-month follow-up

	Fibrosis (N = 33)	Non-fibrosis (N = 114)	P value
Symptomatic patients ratio	30.30% (10/33)	43.86% (50/114)	0.2324
Dyspnea	3.03% (1/33)	1.75% (2/114)	0.8084
exercise limitation	6.06% (2/33)	8.77% (10/114)	0.8887
Cough	18.18% (6/33)	14.91% (17/114)	0.8546
Fatigue	9.09% (3/33)	21.05% (24/114)	0.1910
chest tightness	3.03% (1/33)	7.89% (9/114)	0.5587
Hyposmia	0% (0/33)	1.75% (2/114)	0.9306
Ongoing O_2 requirement	0	0	

Respir Res. 2021 Jul 9;22(1):203.

DLCO in Post-COVID-19 pulmonary fibrosis

- Reduced DLCO: most common impairment in PTFs d/t pulmonary fibrosis in COVID-19 patients with prolonged illness

- Huang et al, n=57(severe: 17, non-sever: 40)
- 30-days after discharge: 50% patients with decreased DLCO

Characteristic	Total (n=57)	Severe (n=17)	Non-severe (n=40)
FEV1 < 80% of pred	5 (8.8)	3 (17.6)	2 (5.0)
FEV1 ≥ 80% of pred	52 (91.2)	14 (82.4)	38 (95.0)
FVC < 80% of pred	6 (10.5)	4 (23.5)	2 (5.0)
FVC ≥ 80% of pred	51 (89.5)	13 (76.5)	38 (95.0)
FEV1 / FVC < 80%	25 (43.9)	9 (52.9)	16 (40.0)
FEV1 / FVC ≥ 80%	32 (56.1)	8 (47.1)	24 (60.0)
TLC < 80% of pred	7 (12.3)	4 (23.5)	3 (7.5)
TLC ≥ 80% of pred	50 (87.7)	13 (76.5)	37 (92.5)
DLCO < 80% of pred	**30 (52.6)**	**13 (76.5)**	**17 (42.5)**
DLCO ≥ 80% of pred	**27 (43.4)**	**4 (23.5)**	**23 (57.5)**

Respir Res. 2020; 21: 163.

DLCO in Post-COVID-19 pulmonary fibrosis

- Liang et al, n=76 (HFNC/NIMV: 2), age: 41.3 year, male: 28%
- 3-month follow-up: all PFT → within normal range

Variables	Values
FEV1	
L	2.9 ± 0.6 (1.4–4.5)
% predicted	98.0 ± 10.8 (64.3–125.4)
FVC	
L	3.7 ± 0.8 (1.9–5.5)
% predicted	107.1 ± 12.3 (79.5–133.6)
FEV1/FVC, %	77.9 ± 5.4 (62.2–95.2)
TLC	
L	5.2 ± 0.8 (3.8–7.1)
% predicted	98.2 ± 9.7 (67.6–120.3)
VC	
L	3.8 ± 0.8 (1.9–5.5)
% predicted	104.9 ± 11.8 (78.0–130.1)
DLCO	
mL/min/kPa	8.0 ± 1.7 (5.3–13.1)
% predicted	89.3 ± 11.5 (63.4–118.4)

J Korean Med Sci. 2020 Dec 07;35(47):e418.

DLCO in Post-COVID-19 pulmonary fibrosis

- Gassel et al, n=48, Survivors after MV applying COVID-19 pneumonia
- Age: 63 years, male: 68.8%
- 3 month after discharge

PFT (*N* = 43)	Absolute Value	Percentage of Predicted	Below LLN
FEV_1, L	2.9 (2.6–3.5)	95.0 (77.0–104.5)	11 (25.6)
FEV_1/VC, %	79.9 (76.1–86.6)	—	0 (0.0)
FVC, L	3.6 (3.1–4.2)	87.0 (70.0–106.0)	16 (37.2)
RV, L	2.0 (1.6–2.2)	88.0 (70.0–103.0)	9 (20.9)
TLC, L	5.6 (4.6–6.7)	84.0 (71.5–102.5)	23 (53.5)
DL_{CO_c}, L‡	5.4 (4.6–6.3)	61.0 (50.0–69.0)	36 (87.8)
6-MWT, m§	480.0 (386.0–536.0)	81.5 (69.5–99.5)	—
MRC Dyspnea score			
Grade 0–1 (none/mild)	27 (62.8)		
Grade 2–3 (moderate)	14 (32.5)		
Grade 4–5 (severe)	2 (4.7)		

Am J Respir Crit Care Med. 2021 Feb 1; 203(3): 371–374.

DLCO and fibrosis

Table 1 Spearman correlation coefficients of radiographic and dyspnoea scores with pulmonary function, 6-minute walk distance, frailty and symptoms

	DLCO (% predicted)			FVC (% predicted)			6MWD (m)		
CT pattern	**R2**	**r**	**P value**	**R2**	**r**	**P value**	**R2**	**r**	**P value**
Ground glass opacities	0.12	−0.34	**0.003***	0.06	−0.25	**0.03***	0	−0.02	0.92
Reticulations	0.41	−0.64	**<0.001***	0.04	−0.21	0.07	0	−0.02	0.8
Traction bronchiectasis	0.24	−0.49	**<0.001***	0.05	−0.23	**0.04***	0	−0.05	0.69
	Frailty phenotype score			**Cough scale**			**UCSD SOBQ**		
CT pattern	**R2**	**r**	**P value**	**R2**	**r**	**P value**	**R2**	**r**	**P value**
Ground glass opacities	0.21	0.46	**<0.001***	0	0.07	0.56	0.02	0.14	0.23
Reticulations	0.05	0.23	**0.04***	0.07	0.26	**0.02***	0	0.05	0.66
Traction bronchiectasis	0.03	0.16	0.17	0.06	0.25	**0.03***	0	0.07	0.57
	DLCO (% predicted)			**FVC (% predicted)**			**6MWD (m)**		
	R2	**r**	**P value**	**R2**	**r**	**P value**	**R2**	**r**	**P value**
UCSD SOBQ	0.02	−0.14	0.24	0.06	−0.25	**0.04***	0.06	−0.25	**0.03***
	Frailty phenotype score			**Grip strength (kg)**			**Gait speed (m/s)**		
	R^2	**r**	**P value**	**R^2**	**r**	**P value**	**R^2**	**r**	**P value**
UCSD SOBQ	0.22	0.47	**<0.001***	0.14	−0.37	**0.001***	0.05	−0.21	0.06

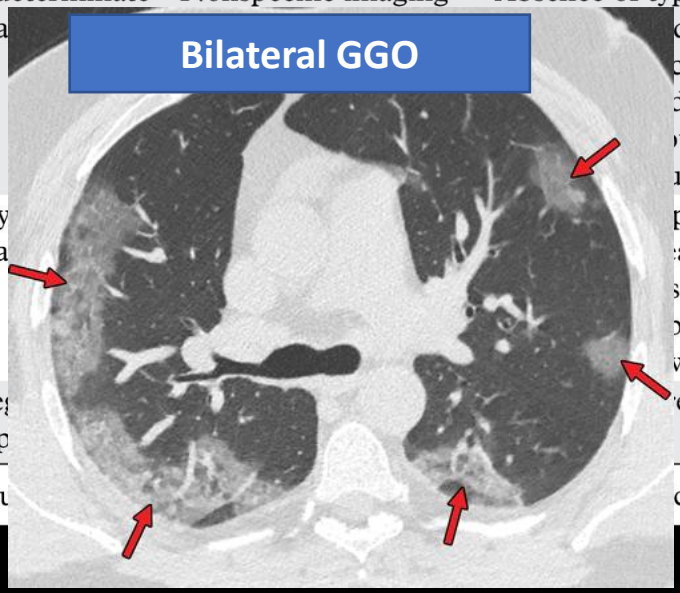
*Significant after controlling for false discovery using the Benjamini-Hochberg method at a false discovery rate of 0.10.
DLCO, diffusion capacity for carbon monoxide; 6MWD, 6-minute walk distance; UCSD SOBQ, University of California San Diego Shortness of Breath Questionnaire.

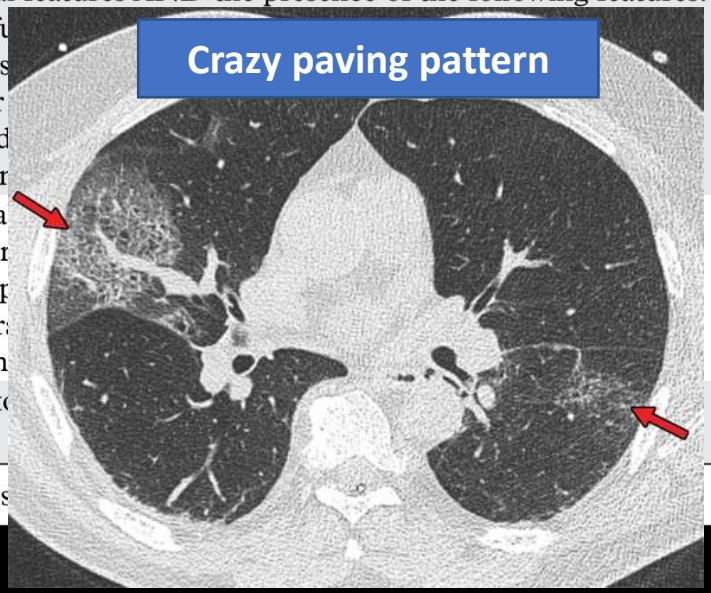
Thorax. 2021 Dec;76(12):1242-1245

COVID-19 and radiological findings

Table 2: Imaging Classification and CT Features of COVID-19 Pneumonia

Imaging Classification	Rationale	CT Features
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia	Peripheral, bilateral, ground-glass opacities with or without consolidation or visible intralobular lines ("crazy-paving" pattern) Multifocal ground-glass opacities of rounded morphology with or without consolidation or visible intralobular lines (crazy-paving pattern) Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)
Indeterminate a	Nonspecific imaging	Absence of typical features AND the presence of the following features:
Aty a		
Neg p		
Sou		





Radiographics. 2020 Nov; 40(7): 1848–1865.

Radiological findings

- Fibrosis: Architectural distortion/Traction bronchiectasis/Parenchymal band/Reticulation/Honeycombing

Fibrosis X

Fibrotic-like lesion

1 month

multiple GGOs,
ial
ing, mild
cal traction
ectasis

nonth

reduced extension,
traction bronchiectasis
(thin arrows)
localized “honeycombing”
(thick arrow) in the
subpleural region

Radiology. 2021 Apr;299(1):E177-E186.

Radiological findings

- Prospective
- 6-month follow-up
- N=114

  (mechanical ventilation

  =3.5%)
- Fibrotic-like changes in 35.1%

Table 3: Comparison of Initial CT Findings and Scores between Groups

Characteristics	All patients(n=114)	Group1 (n=40), fibrotic-like change on CT	Group 2(n=74), no fibrotic-like changes on CT	*P* value	*Adjusted P* value
Time from symptoms onset to CT scan(days)	17±11	19±11	16±11	.16	1.00
Lung involvement					
Unilateral	2/114 (1.8%)	0/40 (0%)	2/74 (2.7%)	.29	1.00
Bilateral	112/114 (98%)	40/40 (100%)	72/74 (97%)		
Predominant CT pattern					
GGO	71/114 (62%)	25/40 (63%)	46/74 (62%)	.97	1.00
Consolidation	27/114 (24%)	9/40 (23%)	18/74 (24%)		
Reticulation	16 /114 (14%)	6/40 (15%)	10/74 (14%)		
Presence of nodule or mass	3/114 (2.6%)	2/40 (5%)	1/74 (1.4%)	.28	1.00
Pleural effusion	10/114 (8.8%)	6/40 (15%)	4/74 (5.4%)	.10	1.00
Emphysema	2/114 (1.8%)	2/40 (5%)	0/74 (0%)	.12	1.00
Thickening of the adjacent pleura	40/114 (35%)	22/40 (55%)	18/74 (24%)	.001	.02
Interlobar pleural traction	27/114 (24%)	14/40 (35%)	13/74 (18%)	.06	1.00
Honeycombing	2/114 (1.8%)	2/40 (5%)	0/74 (0%)	.12	1.00
Bronchiectasis	12/114(10.5%)	9/40 (23%)	3/74 (4.1%)	.004	.07
CT score					
Total lesions	15 (9)	20 (5.5)	13 (7)	<.001	<.001
⩾18	76/114 (67%)	17/40 (43%)	59/74 (80%)	<.001	.001
<18	38/114 (33%)	23/40 (58%)	15/74 (20%)		
GGO	10 (10)	16 (10)	10 (8)	.001	.02
Consolidation	5 (8)	7 (5.5)	4 (8)	.004	.07
Reticular	5 (7)	5 (6.5)	3.5 (6)	.01	.16

Radiology. 2021 Apr;299(1):E177-E186.

Radiological findings

Prospective, 6-month follow-up, N=118 (MV+NIV: 74%)

Fibrotic like changes (reticulation, HC) = 85 (72%)

Comparison between baseline and follow-up chest CT findings in patients with COVID-19

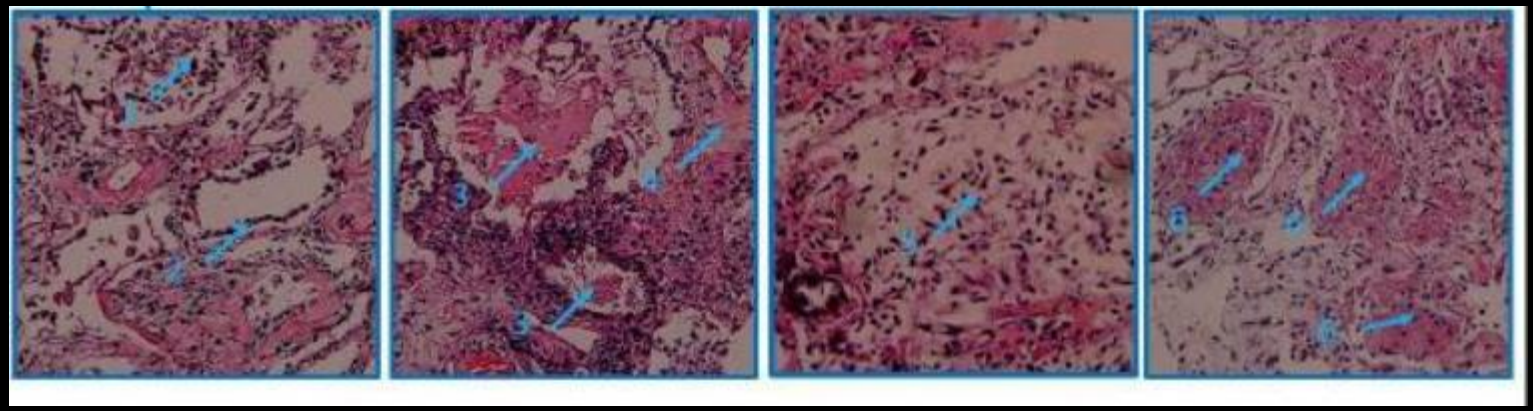
CT Finding	Baseline	Six-month Follow-up	*P* Value
GGO pattern	102 (86)	49 (42)	<.001
Predominantly linear	54 (46)	47 (40)	.38
Round	24 (20)	2 (2)	<.001
Crazy paving	24 (20)	0 (0)	<.001
GGO location (peripheral)	96 (81)	40 (34)	<.001
Multilobe involvement (two or more lobes)	96 (81)	45 (38)	<.001
Total lobar involvement	80 (68)	16 (14)	<.001
Bilateral distribution	94 (80)	33 (28)	<.001
Posterior (lung) involvement by GGO and/or consolidation	94 (80)	16 (14)	<.001
Consolidative opacities	80 (68)	2 (2)	<.001
Interlobular septal thickening	62 (53)	33 (28)	.007
Fibrosis-like changes	65 (55)	85 (72)	<.001

CT Finding	Baseline	Six-month Follow-up	*P* Value
Bronchiectasis	40 (34)	29 (25)	.23
Air bronchogram	38 (32)	0 (0)	<.001
Bronchial wall thickening	36 (31)	5 (4)	<.001
Pulmonary nodules surrounded by GGOs	18 (15)	0 (0)	<.001
Halo sign	11 (9)	0 (0)	.002
Reversed halo sign	11 (9)	0 (0)	.08
Pericardial effusion	27 (23)	16 (14)	.13
Pleural effusion	20 (17)	2 (2)	<.001
Lymphadenopathy	31 (26)	5 (4)	<.001
Enlargement, subsegmental arteries and veins (≥3 mm)	109 (92)	82 (69)	.07
Pulmonary trunk diameter (<31 mm)	98 (83)	98 (83)	.99

Radiology . 2021 Nov;301(2):E396-E405.

Pathological findings

Acute (6 days after Sx onset): acute and organizing **diffuse alveolar damage (DAD)**



- Denuded alveolar lining cells (arrow 1)
- Reactive type II pneumocyte hyperplasia (arrow 2)
- Intra-alveolar fibrinous exudates (arrow 3)
- loose interstitial fibrosis and chronic inflammatory infiltrates (arrow 4).
- Intra-alveolar loose fibrous plugs of organizing pneumonia (arrow 5)
- intra-alveolar organizing fibrin seen in most foci (arrow 6)

Ann Intern Med. 2020 Mar 12 : M20 0533.

Pathological findings

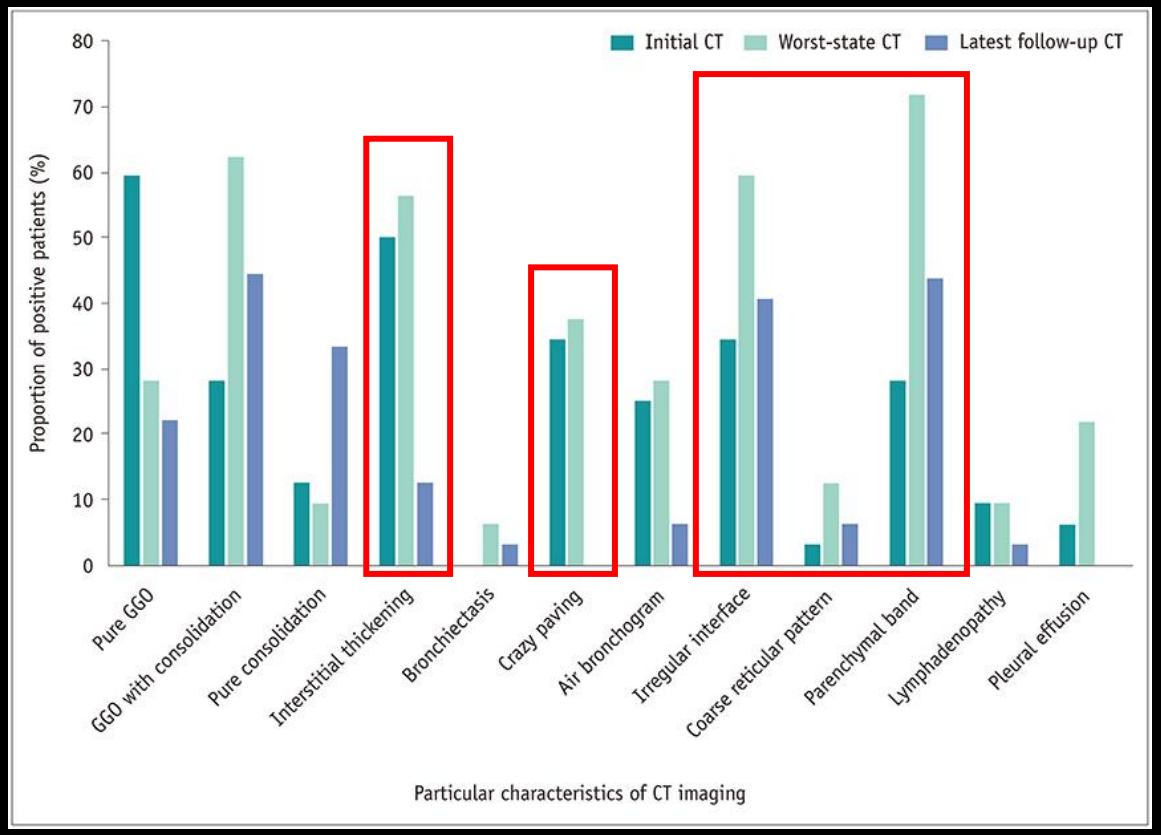
- 30 autopsy cases with COVID-19 infection
- Wuhan, China, February and March, 2020
- duration of illness ranged: median = 42 days (range: 16-82 days)
- diffuse DAD: 28 (93.3%)
  - ✓acute (32%), organizing (25%) and/or fibrosing (43%) patterns
- Patients who progressed to fibrosing DAD: prolonged clinical course (≥ 4 weeks) and duration of mechanical ventilation (median 20 days)

Histopathology. 2021 Mar;78(4):542-555

Prognosis

Short-term follow-up

- COVID-19 patients (=32), Zhongnan Hospital of Wuhan University between January 5, 2020 and February 16, 2020
- Median time from discharge to fu CT: 9 days



Typical features of COVID-19 pneumonia
➔ almost resolved
Fibrosis
➔ still obvious in FU CT

Yu et al, Korean J Radiol. 2020 Jun;21(6):746-755.

Short-term follow-up

- prospective, 3-month follow-up, COVID-19 health care workers (n=76)
- 69 (91%) had returned to their original work
- HRCTs: returned to normal in most of the patients (82%)
- Mean FEV1, FVC, FEV1/FVC, TLC, DLCO: all normal (> 80% predicted)
- 42% of survivors had mild pulmonary function abnormalities
  - ✓ FEV1: 4 (5%) , DLCO: 15 (20%)

Groups	No.	FEV1 % pred	FVC % pred	FEV1/FVC ratio	TLC % pred	VC % pred	DLCO % pred
0	30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	± 11.7
1	20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	± 12.3
2	15	95.2 ± 7.6	99.3 ± 5.2	81.5 ± 5.3	94.3 ± 9.3	98.0 ± 6.3	84.5 ± 8.8
3	11	82.6 ± 9.5	88.7 ± 4.3	79.5 ± 8.6	87.3 ± 8.6	87.7 ± 5.3	86.4 ± 10.9
P value		< 0.001	< 0.001	0.003	< 0.001	< 0.001	0.154

Dyspnea scores correlated well with measurements of a panel of pulmonary function parameters except for DLCO

J Korean Med Sci. 2020 Dec 7;35(47):e418.

Mid-term follow-up

- 90-150 days follow-up, n=288 (mechanical ventilator=3.1%)
- Shenzhen Third People's Hospital from January 11, 2020 to April 26, 2020

- Dynamic changes of pulmonary fibrosis in 457 patients at different stages after the onset of COVID-19

COVID-19 Patients	Days after onset				
	0–30	31–60	61–90	91–120	> 120
Patients included	457	418	279	207	79
Patients with pneumonia	428 (93.65%)	397 (94.98%)	272 (97.49%)	202 (97.58%)	77 (97.47%)
Patients with pulmonary fibrosis	397 (86.87%)	311 (74.40%)	222 (79.57%)	141 (68.12%)	49 (62.03%)
Patients with resolution of pulmonary fibrosis	18 (4.53%)	49 (13.61%)	14 (6.31%)	30 (21.28%)	15 (30.61%)
Overall pulmonary fibrosis			**397 (86.87%)**		
Overall resolution of fibrosis			**126 (31.74%)**		

* Definition of fibrosis: combination of findings including parenchymal bands, irregular interfaces, reticulation and traction bronchiectasis

Respir Res . 2021 Jul 9;22(1):203.

Mid-term follow-up

- 90-150 days follow-up, n=288 (mechanical ventilator=3.1%)
- Shenzhen Third People's Hospital from January 11, 2020 to April 26, 2020

- CT imaging features in 457 patients at different stages after the onset of COVID-19

COVID-19 Patients	Days after onset				
	0–30	31–60	61–90	91–120	> 120
Ground-glass opacities (GGO)	88.66% (352/397)	90.76% (275/303)	91.41% (149/163)	75.58% (65/86)	65.31% (32/49)
	(327/397)	(287/303)	(156/163)	(84/86)	(46/49)
Irregular interface	26.45% (105/397)	25.41% (77/303)	25.15% (41/163)	22.09% (19/86)	28.57% (14/49)
Traction bronchiectasis	5.54% (22/397)	14.52% (44/303)	19.02% (31/163)	16.28% (14/86)	14.29% (7/49)

Peaks in 2-3 month ➔ stable or slightly resolution

Respir Res . 2021 Jul 9;22(1):203.

long-term follow-up

- 6, 12 month follow-up, n=1276 survivors (mechanical ventilator=1%)
- Jin Yin-tan Hospital (Wuhan, China) between Jan 7 and May 29, 2020

- Chest CT among COVID-19 patients at 6-month and 12-month follow-up according to severity scale

	Scale 3: not requiring O2 (N=318)			Scale 4: requiring O2 (N=864)			Scale 5–6: requiring HFNC, NIV, or IMV (N=94)		
	6 month	12 month	p value	6 month	12 month	p value	6 month	12 month	p value
No.	33	28		56	52		39	38	
At least one abnormal CT pattern	33 (100%)	11 (39%)	<0·0001	56 (100%)	21 (40%)	<0·0001	39 (100%)	33 (87%)	0·025
GGO	28 (85%)	11 (39%)	0·0047	52 (93%)	14 (27%)	<0·0001	32 (82%)	29 (76%)	NS
Irregular lines	6 (18%)	6 (21%)	NS	13 (23%)	12 (23%)	NS	NS	23 (61%)	0·22
Subpleural line	5 (15%)	1 (4%)	NS	1 (2%)	2 (4%)	NS	3 (8%)	8 (21%)	0·06
Interlobular septal thickening	1 (3%)	0 (0%)	NS	2 (4%)	1 (2%)	NS	0 (0%)	4 (11%)	0·046
Reticular pattern	0 (0%)	0 (0%)	NA	0 (0%)	1 (2%)	NS	1 (3%)	3 (8%)	NS
Consolidation	0 (0%)	0 (0%)	NA	4 (7%)	0 (0%)	0·08	0 (0%)	1 (3%)	NS

Lancet. 2021 28 August-3 September

long-term follow-up

- 6, 12 month follow-up, n=1276 survivors (mechanical ventilator=1%)
- Jin Yin-tan Hospital (Wuhan, China) between Jan 7 and May 29, 2020

- PFT among COVID-19 patients at 6-month and 12-month follow-up according to severity scale

	Scale 3: not requiring O2 (N=318)			Scale 4: requiring O2 (N=864)			Scale 5–6: requiring HFNC, NIV, or IMV (N=94)		
	6 month	12 month	p value	6 month	12 month	p value	6 month	12 month	p value
No.	59	56		125	118		70	70	59
FEV_1 <80% of predicted	4 (7%)	2 (4%)	NS	2 (2%)	3 (3%)	NS	10 (14%)	4 (6%)	0·014
FVC <80% of predicted	3 (5%)	2 (4%)	<0·0001	0 (0%)	2 (2%)	NS	9 (13%)	6 (9%)	0·08
FEV_1/FVC <70%	5 (8%)	4 (7%)	NS	11 (9%)	6 (5%)	NS	2 (3%)	0 (0%)	NS
TLC <80% of predicted	6/57 (11%)	3 (5%)	NS	12/124 (10%)	8/117 (7%)	NS	27/69 (39%)	20 (29%)	0·021
FRC <80% of predicted	4/57 (7%)	6 (11%)	NS	5/124 (4%)	5/116 (4%)	NS	14/67 (21%)	16 (23%)	NS
RV <80% of predicted	12/57 (21%)	15 (27%)	NS	18/124 (15%)	26/117 (22%)	0·050	34/69 (49%)	44 (63%)	NS
DLCO <80% of predicted	12/57 (21%)	13 (23%)	NS	32/124 (26%)	36/117 (31%)	NS	39/69 (57%)	38 (54%)	NS

Biomarkers

- Potential biomarkers for risk of developing post-COVID-19 pulmonary fibrosis

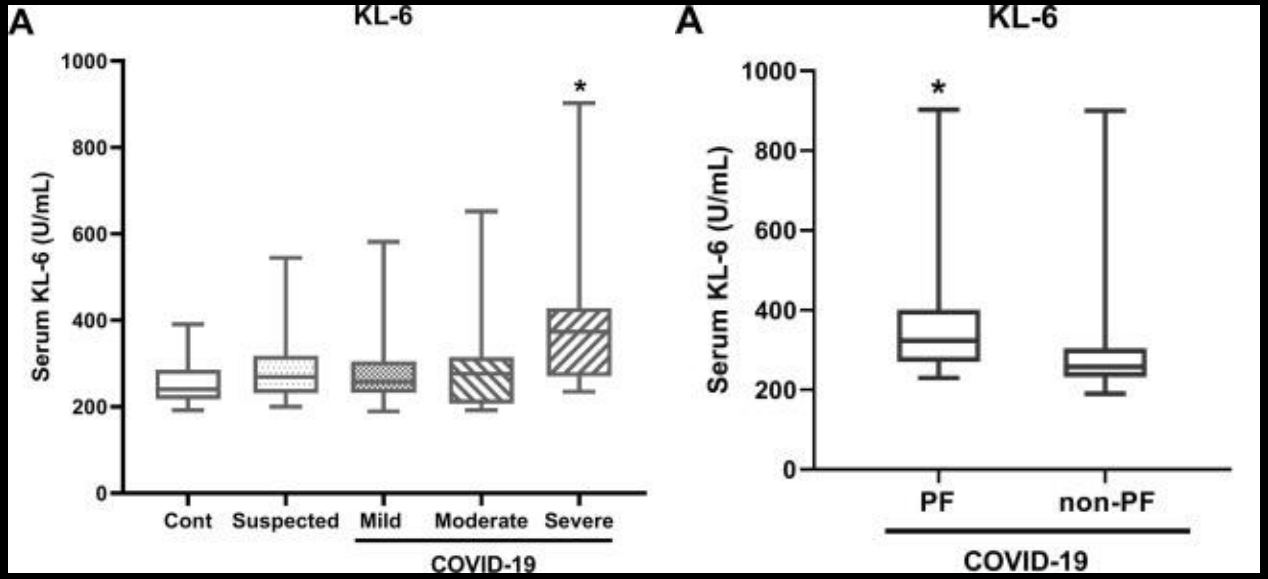
Acute COVID-19	Follow-up period
• C-reactive protein	• TNF-α
• Lymphocyte count	• IL-17A, IL-17D
• LDH	• VCAM-1, ICAM-1, PlGF
• IFN-γ	• KL-6
• MMP-9	
• sST2	

ICAM-1, intercellular adhesion molecule-1; IL-17, interleukin-17; IFN-γ, interferon-gamma; LDH, lactate dehydrogenase; MMP-9, metalloproteinase-9; PlGF, placental growth factor; sST2, soluble suppressor of tumorigenicity 2; VCAM-1, vascular cell adhesion molecule-1.

Clin Chem Lab Med. 2021 Nov 16;60(3):307-316.

Alveolar epithelial cells damage biomarkers: KL-6

- **A Krebs Von Den Lungen Antigen (KL-6)**
- type II pneumocytes, destruction & regeneration of the air-blood barrier
- ↑ various respiratory diseases, particularly in ARDS, ILDs, or IPF
- Retrospective, n=113, CT follow-up at discharge/blood sample at ADM



	Mild	Moderate	Severe	Total
Total	49	28	36	113
fibrosis	2	4	13	19
Ratio, %	4.08	14.29	36.11*	16.81

Clin Chim Acta. 2021 Jun; 517: 48–53.

Treatment and rehabilitation

Anti-fibrotics

- Similarities of pulmonary fibrosis' pathophysiological mechanisms between IPF and COVID-19 infection
- Pirfenidone/nintedanib

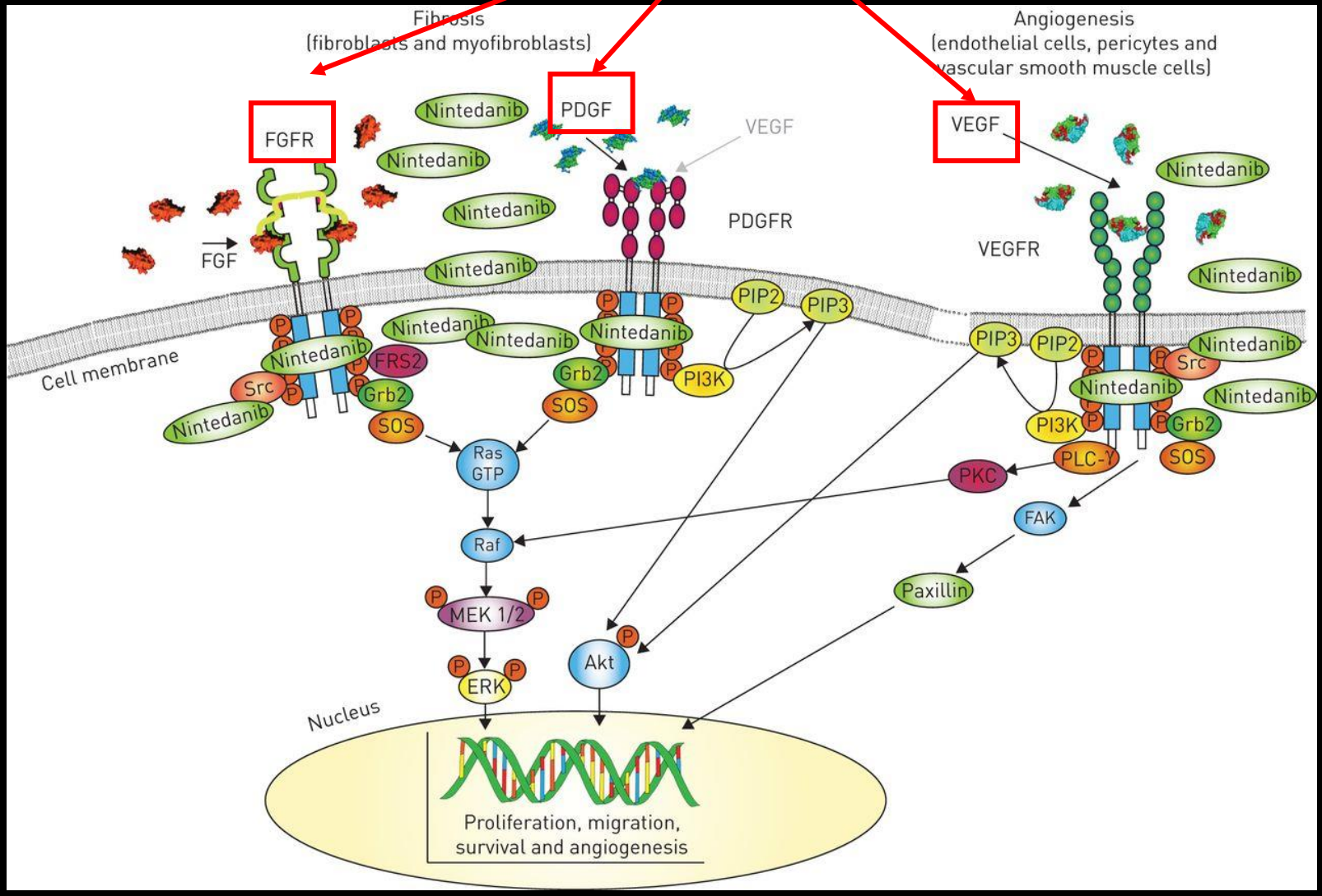
- **Ongoing clinical trials of anti-fibrotic therapy and COVID-19 (Phase 4)**

Clinical Trial number	Location	Status	Intervention
NCT04818489	Egypt	Phase 4, recruiting	Drug: Colchicine 0.5 MG
NCT04912011	Poland	Phase 4, recruiting	Drug: Canrenoate Potassium
NCT04619680	USA	Phase:4, recruiting	Drug: Nintedanib
NCT04856111	India	Phase 4	Drug: Pirfenidone Drug: Nintedanib

Eur Respir J. 2015 May; 45(5): 1434–1445.

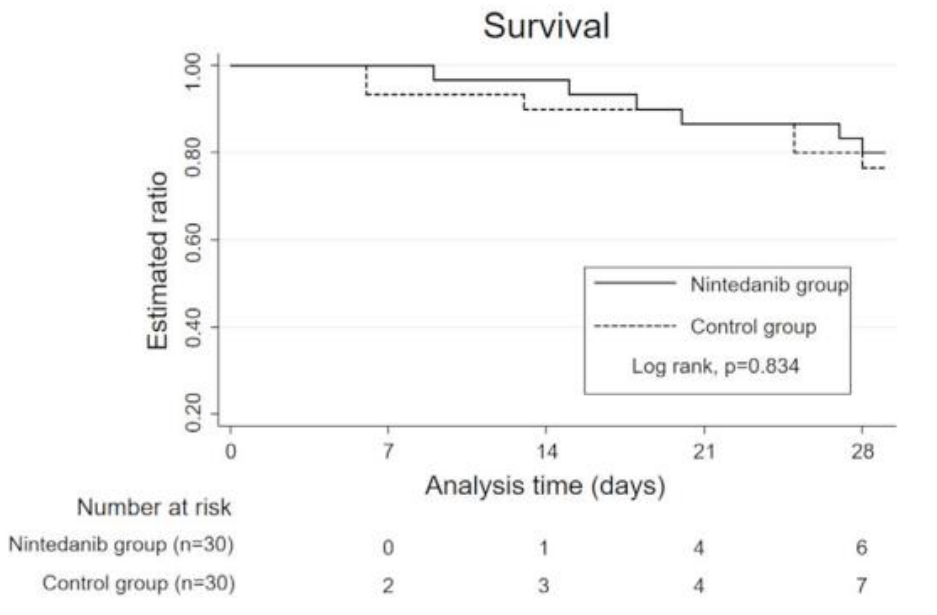
Nintedanib

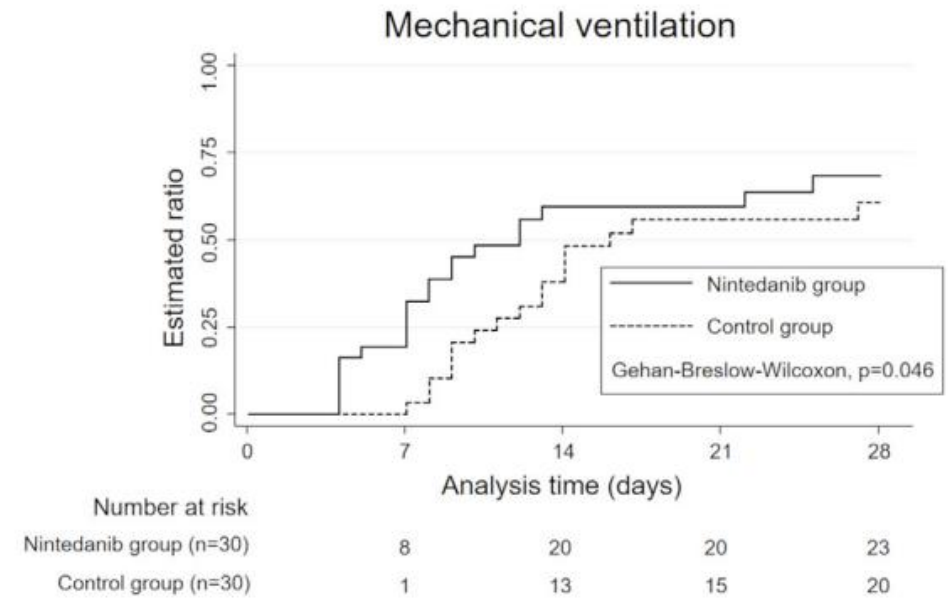
Elevated in COVID-19 patients



Nintedanib

- Interventional study
- adult patients with COVID-19 requiring mechanical ventilation
- nintedanib (n=30) vs age, gender matched control (n=30)
- 150 mg twice per day, from day 1 to exutubation within 28 days





Int J Infect Dis. 2021 Jul;108:454-460.

Nintedanib

- Interventional study
- adult patients with COVID-19 requiring mechanical ventilation
- nintedanib (n=30) vs age, gender matched control (n=30)

	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.

Int J Infect Dis. 2021 Jul;108:454-460.

Alternative treatment

- **Prolonged use of corticosteroids**: might be beneficial for those with radiological pattern suggestive or pathology compatible with organizing pneumonia
  - ✓ In the controlled RECOVERY trial, the use of dexamethasone at a dose of 6 mg per day for up to 10 days for hospitalized patients with COVID-19 receiving respiratory support resulted in lower 28-day-mortality, although the study has not assessed long-term outcomes.
- **Tocilizumab**, a humanized monoclonal antibody against IL-6: reduced risk of progression to MV
- **Spironolactone**: Anti-inflammatory
  - ✓ 1) to increase the circulating levels of ACE-2 and prevent the entry of SARS-CoV-2 into the cells; 2) to block the mineralocorticoid receptor; 3) antiandrogenic activity through downregulation of transmembrane serine protease 2 (TMPRSS2); 4) anti-inflammatory, antioxidant, antifibrotic and antiviral properties
- **Treatment with mesenchymal stem cells (MSCs**) : reduce the immunological response to COVID-19
- **Lung transplantation**

Rehabilitation

- Randomized controlled trial (RCT)
- Hainan General Hospital central hospital and Huanggang Central hospital from January 1, 2020 to February 6, 2020
- Inclusion Criteria: (1) with a definite diagnosis of COVID-19; (2) aged 65 years or above; (3) ≥ 6 months after the onset of other acute diseases; (4) mini-mental state examination (MMSE) score > 21; (6) no COPD or any other respiratory disease; and (7) forced expiratory volume in 1 s (FEV1) ≥ 70%
- Exclusion criteria: (1) moderate or severe heart disease (Grade III or IV, New York Heart Association); (2) with severe ischemic or hemorrhagic stroke or neurodegenerative diseases
- Aim: To investigate the effects of 6-week respiratory rehabilitation training on respiratory function, QoL, mobility and psychological function in elderly patients with COVID-19

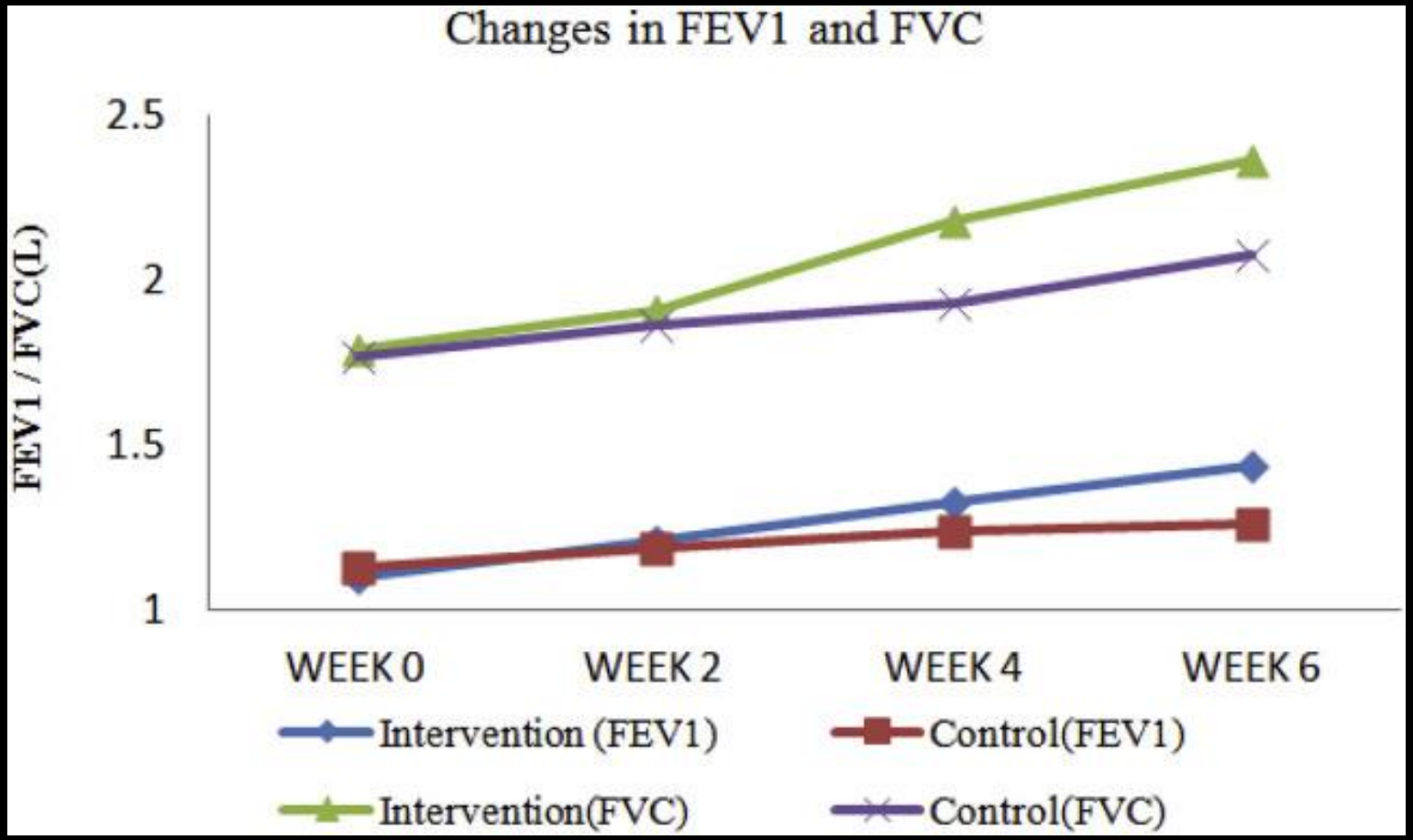
Complement Ther Clin Pract. 2020 May; 39: 101166.

Rehabilitation

Characteristics	Intervention group (n = 36)	Control group (n = 36)
Male, n, %	24 (66.7)	25 (69.4)
Age, years, (M±SD)	69.4 (8.0)	68.9 (7.6)
BMI, kg/m^2, (M±SD)	23.1 (3.5)	22.9 (3.9)
CT features of lung lesions		
Multilobular lesion	25 (69.4)	23 (63.9)
Unilobar lesion	11 (30.6)	13 (36.1)
Pleural effusion	4 (11.1)	3 (8.3)
Comorbidity		
Hypertension	10 (27.8)	8 (22.2)
Type 2DM	9 (25.0)	9 (25.0)
Osteoporosis	8 (22.2)	6 (16.7)

Complement Ther Clin Pract. 2020 May; 39: 101166.

Rehabilitation



Complement Ther Clin Pract. 2020 May; 39: 101166.

Rehabilitation

Measures	Intervention group (n = 36)		Control group (n = 36)	
	Pre	Post	6 weeks ago	After 6 weeks
Pulmonary Function Test				
FEV1(L)	1.10 ± 0.08	1.44 ± 0.25*#	1.13 ± 0.14	1.26 ± 0.32
FVC(L)	1.79 ± 0.53	2.36 ± 0.49*#	1.77 ± 0.64	2.08 ± 0.37
FEV1/FVC%	60.48 ± 6.39	68.19 ± 6.05*#	60.44 ± 5.77	61.23 ± 6.43
TLCO %	60.3 ± 11.3	78.1 ± 12.3*#	60.7 ± 12.0	63.0 ± 13.4
Exercise Capacity Test				
6MWT, m	162.7 ± 72.0	212.3 ± 82.5*#	155.7 ± 82.1	157.2 ± 71.7
ADL				
FIM	109.2 ± 13	109.4 ± 11.1	109.3 ± 10.7	108.9 ± 10.1
QoL (SF-36)				
Physical health	52.4 ± 6.2	71.6 ± 7.6*#	53.2 ± 7.7	54.1 ± 7.5
Body role function	61.2 ± 6.6	75.9 ± 7.9*#	61.3 ± 7.2	62.0 ± 7.3
Physical pain	63.5 ± 7.4	78.3 ± 7.8*#	63.5 ± 8.1	62.9 ± 7.9
General health	61.8 ± 7.7	74.2 ± 7.9*#	61.8 ± 8.4	61.4 ± 6.9
Energy	60.6 ± 6.9	75.6 ± 7.1*#	60.5 ± 7.1	61.2 ± 6.3
Social function	59.4 ± 7.2	69.8 ± 6.4*#	59.5 ± 7.0	58.9 ± 6.6
Emotional role function	61.4 ± 6.9	75.7 ± 7.0*#	61.4 ± 7.3	60.8 ± 7.3
Mental health	61.5 ± 6.5	73.7 ± 7.6*#	61.6 ± 7.2	62.1 ± 7.6
Anxiety and depression assessment				
SAS score	56.3 ± 8.1	47.4 ± 6.3*#	55.8 ± 7.4	54.9 ± 7.3
SDS score	56.4 ± 7.9	54.5 ± 5.9	55.9 ± 7.3	55.8 ± 7.1

Compared with the same group* or control group# after intervention, $P < 0.05$

Rehabilitation

Meta analysis: 24 systematic reviews, 11 RCTs, 8 qualitative studies

- Progressive exercise programmes delivered in ICU can improve functional independence
- Exercise may increase aerobic capacity in younger patients following hospital discharge but for those middle and older age the findings are inconclusive.
- There is inconclusive evidence for NMES in ICU. For older patients in a sub-acute hospital setting, muscle strength may improve with NMES.
- Exercise and mobility training or early mobilisation +/- NMES in ICU can improve muscle strength and independent walking.
- Exercise and mobility training supervised by carers in the home may improve respiratory function.
- Early mobilisation in ICU may reduce ICU-AW and improve functional ability and walking. The optimal time to commence early mobilisation is between 72 and 96 hours of starting mechanical ventilation.
- Nutritional supplementation combined with rehabilitation may improve performance in activities in daily living in post-ICU hospital settings
- This evidence could be generalizable to those with, or recovering from, COVID-19 who required critical care.

NMES: neuromuscular electrical stimulation; ICU-AW: ICU–Acquired weakness

Physiotherapy. 2021 Jun; 111: 4–22.

Take home messages

- Post-COVID-19 pulmonary fibrosis is defined as the presence of persistent and different fibrotic tomographic changes identified on follow-up, often combined with impairment in pulmonary function tests.

- The incidence of post COVID-19 fibrosis has been reported to vary from 20 to 70%, depending on the severity of the disease, the definition of fibrosis and the follow-up duration of the study

- The prevalence, pathophysiology, and management of post-COVID-19 pulmonary fibrosis remain poorly understood and need to be thoroughly investigated. Future studies are necessary to better understand all issues regarding pulmonary fibrosis secondary to COVID-19.

Thank you for attention

Q & A