
بسم الله الرحمن الرحیم

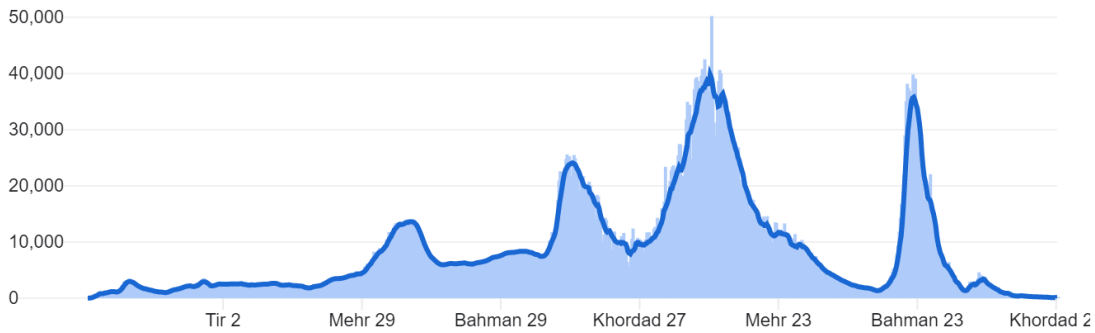
Post COVID pulmonary complication

Dr Ramin Sami
Pulmonologist
IUMS

Introduction

From JHU CSSE COVID-19 Data · Last updated: 1 day ago

Iran | All time



Cases overview

From Our World in Data and JHU CSSE COVID-19 Data
updated: 2 days ago

Iran

Total cases	Deaths
7.23M	141K

Worldwide

Total cases	Deaths
536M	6.31M
+491K	+1,009

Post COVID

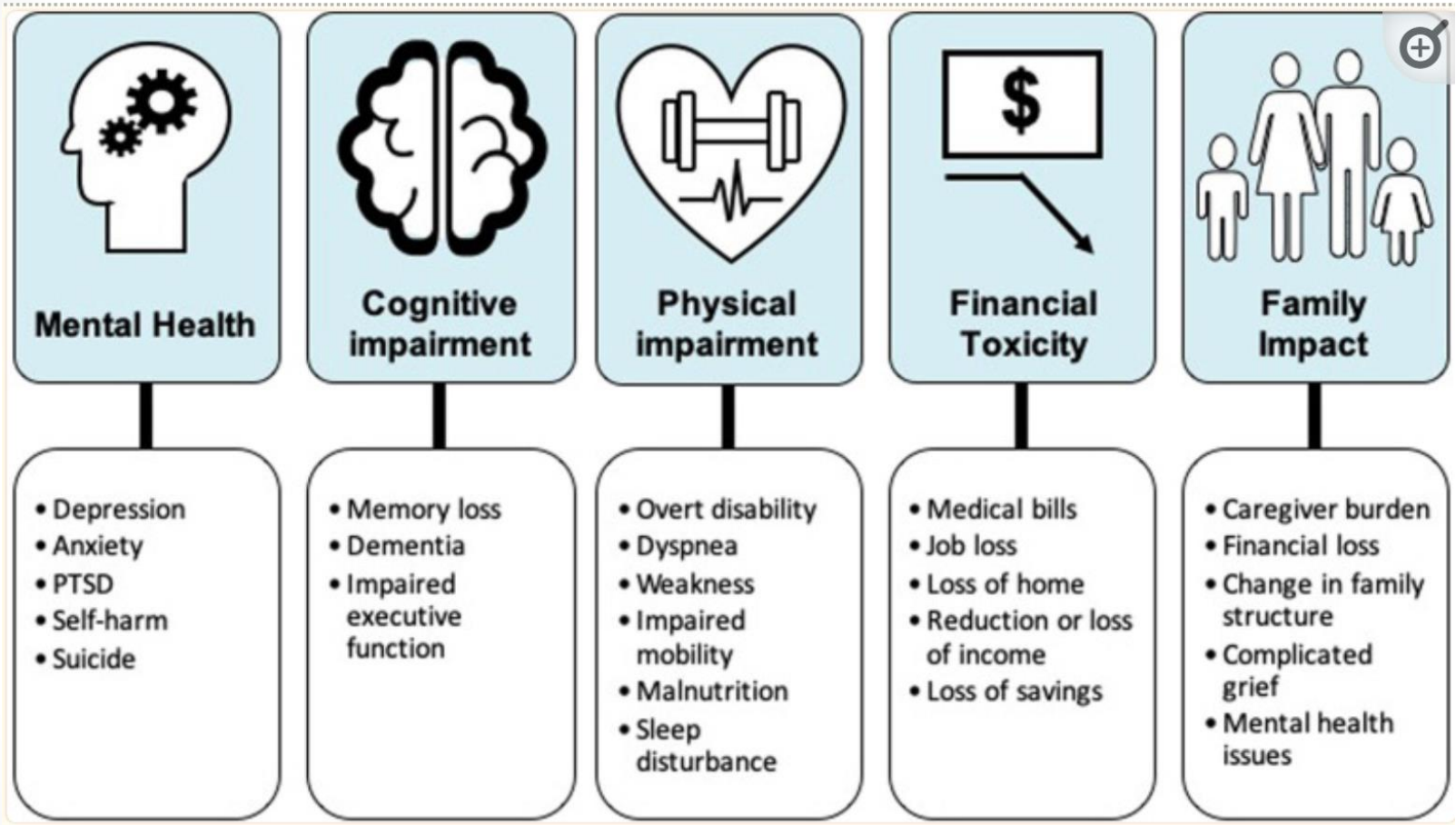
- Post acute sequelae of SARS-CoV-2 infection (PASC)
- Post intensive care syndrome (PICS)
- Long COVID

- Discharge is not the end of treatment

Box 1: Clinical case definitions to identify and diagnose the long-term effects of COVID-19[1]

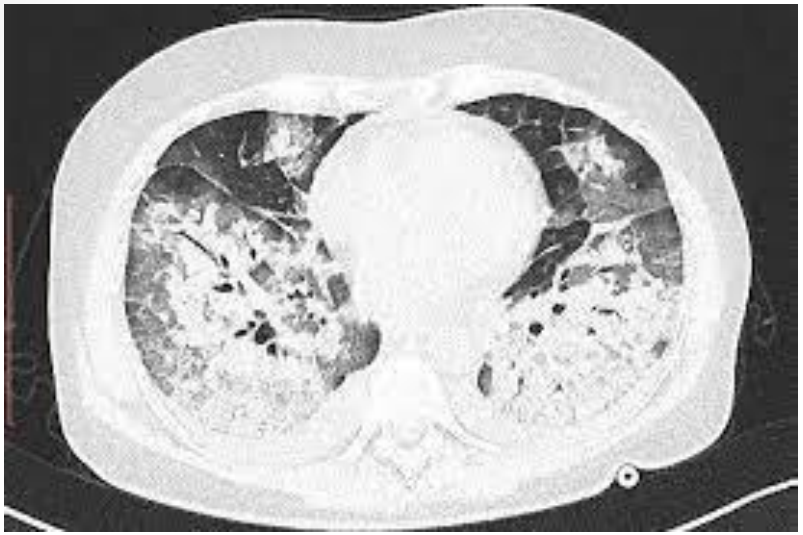
- **Acute COVID-19**: signs and symptoms of COVID-19 for up to 4 weeks
- **Ongoing symptomatic COVID-19**: signs and symptoms of COVID-19 from 4 weeks up to 12 weeks
- **Post-COVID-19 syndrome**: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

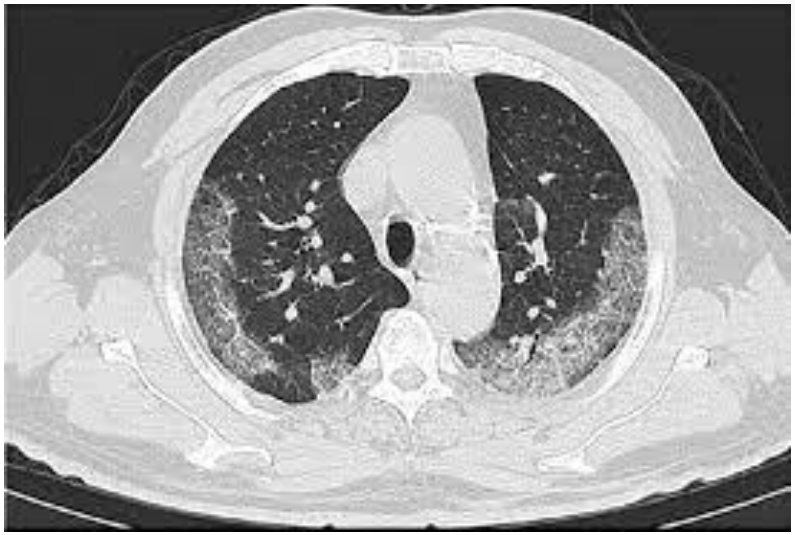
In addition to the clinical case definitions, the term 'long COVID' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more).

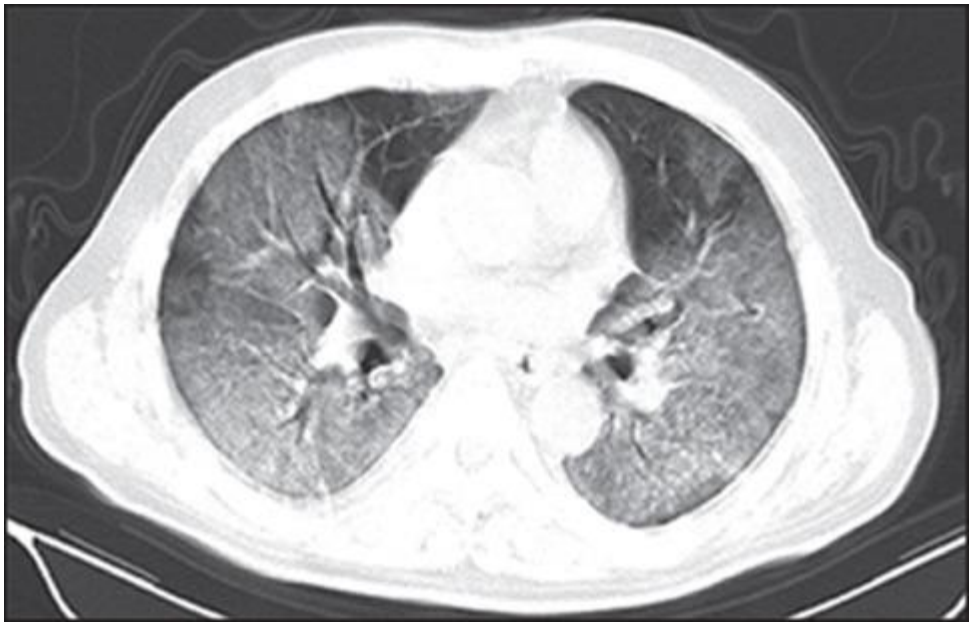

Mental Health
• Depression
• Anxiety
• PTSD
• Self-harm
• Suicide
Cognitive impairment
• Memory loss
• Dementia
• Impaired executive function
Physical impairment
• Overt disability
• Dyspnea
• Weakness
• Impaired mobility
• Malnutrition
• Sleep disturbance
$
Financial Toxicity
• Medical bills
• Job loss
• Loss of home
• Reduction or loss of income
• Loss of savings
Family Impact
• Caregiver burden
• Financial loss
• Change in family structure
• Complicated grief
• Mental health issues

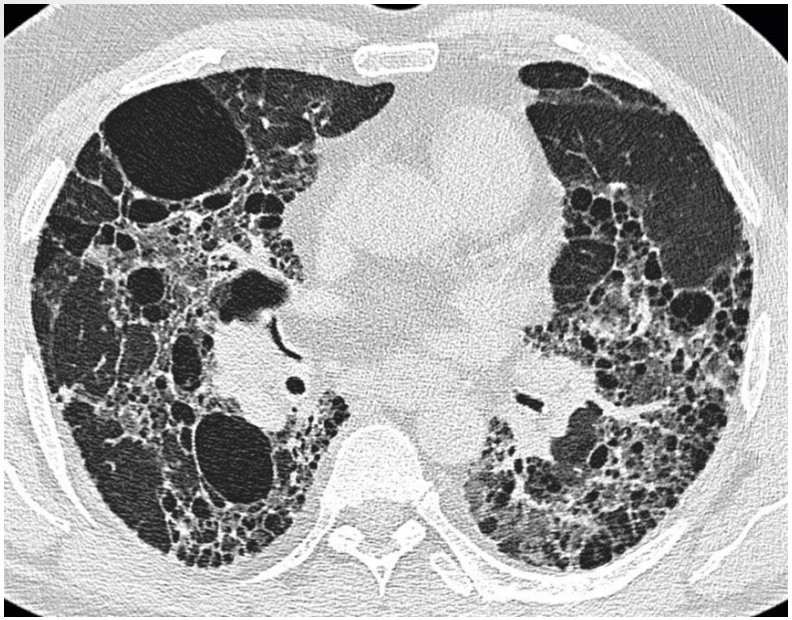
Post COVID ……..

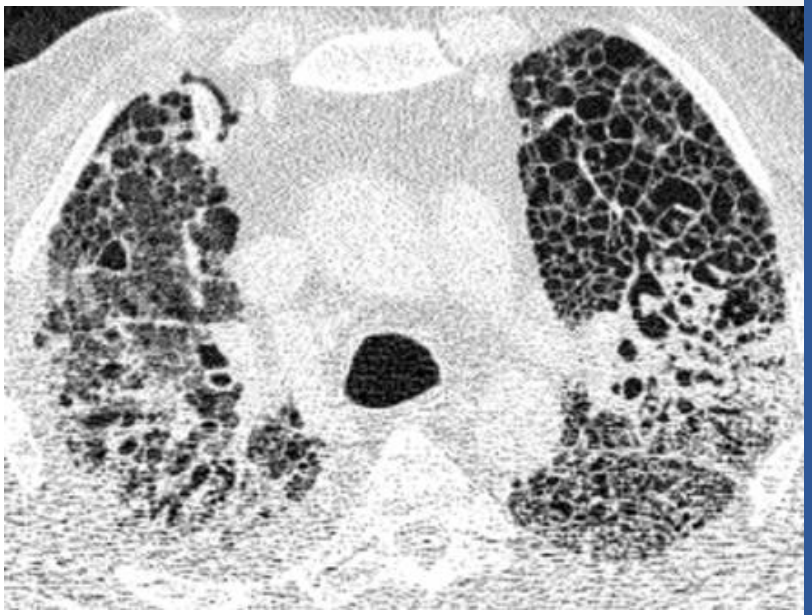
1. Pulmonary fibrosis
2. Pulmonary ILD
3. Pulmonary diffuse parenchymal lung disease (PDPLD)
4. Pulmonary sequel

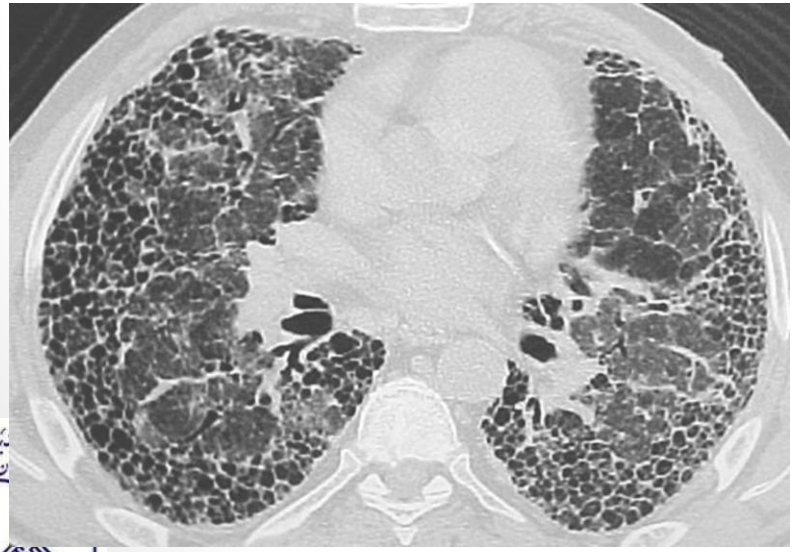


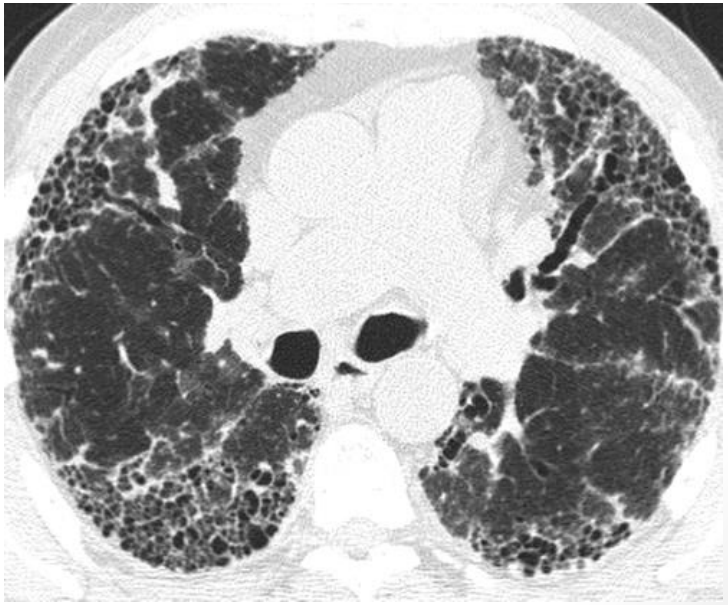






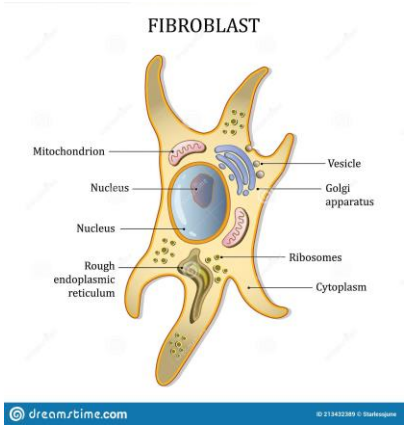






Pathogenesis

- Fibroblast
- Lymphocyte
- Collagen
- .....
- Is it due to ARDS or pneumonia?



Pathogenesis

- The SARS-CoV-2 virus may induce lung fibrosis by at least four proposed mechanisms:

1. COVID-19 ARDS causing lung fibrosis
2. Mechanical stretch of alveolar epithelial cells during MV
3. Excess oxygen-free radicals due to prolonged use of high oxygen
4. Viral-induced lung fibrogenesis
   - Virus-induced alveolar epithelial cell lung injury
   - Abnormal immune response
   - Direct stimulation of TGF-b

Pathogenesis

- Diffuse alveolar damage occurs in COVID-19-associated ARDS, which is characterized by:

1. Exudative phase with edema, hyaline membrane formation, and interstitial acute inflammation
2. Organizing phase with loose organizing fibrosis mostly within the alveolar septa and type 2 pneumocyte hyperplasia.
3. Potential fibrotic stage which can either resolve completely or progress to fibrosis

Pathology

Usual interstitial pneumonia	**n = 9**
Definite UIP	5
Probable UIP	1
Definite UIP with superimposed ALI	2
Indeterminate for UIP[a]	1
Acute lung injury	**5**
Persistent DAD or organizing ALI with fibrosis	3
Chronic bronchiolitis with organizing pneumonia	2
Other	**4**
Desquamative interstitial pneumonia	1
Acute and organizing bronchopneumonia	1
Mild nonspecific abnormalities of uncertain significance	2

K.E. Konopka et al. / EClinicalMedicine 42 (2021)

Pathology

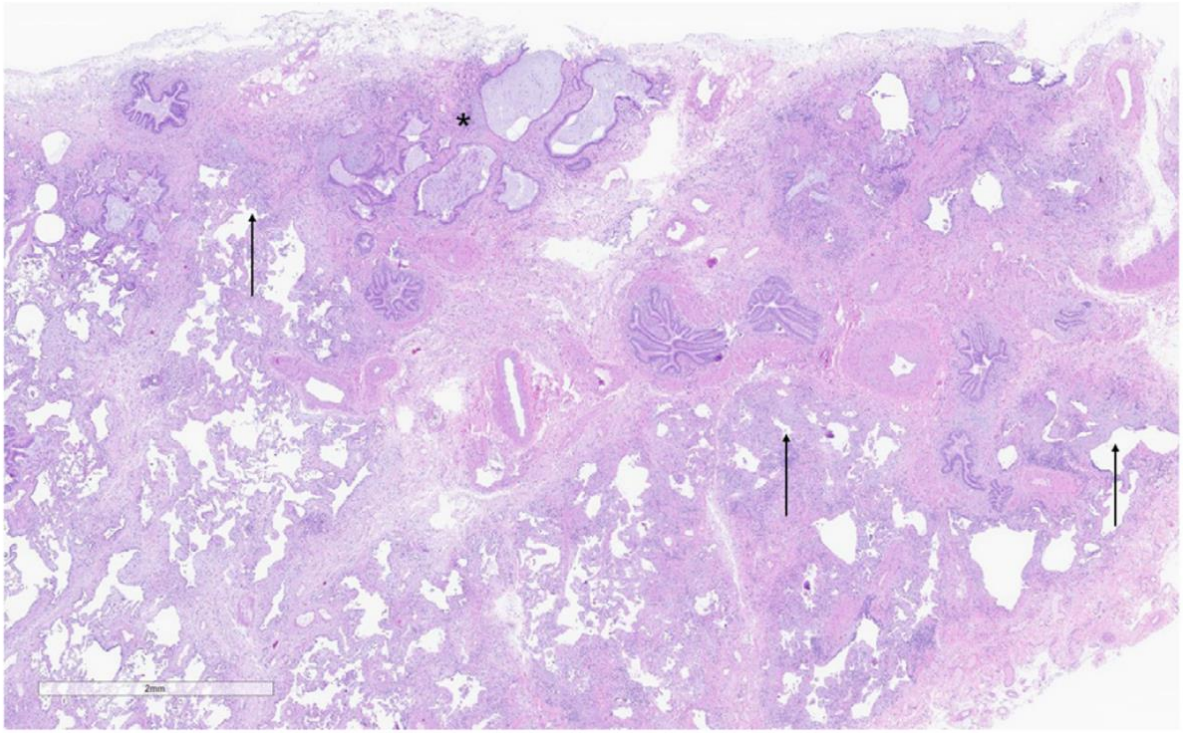


Figure 1. Cases diagnosed as definite usual interstitial pneumonia showed a characteristic pattern of "patchwork" fibrosis, comprised mainly of dense collagen deposition with scattered fibroblastic foci (arrows). The fibrosis resulted in architectural distortion in the forms of both scarring and microscopic honeycomb change (asterisk). Hematoxylin and eosin-stained slide; magnification 16x.

K.E. Konopka et al. / EClinicalMedicine 42 (2021)

Pathology

TABLE 4
Characteristics of Patients With and Without UIP

	UIP cohort (n = 9)	Patients without UIP (n = 9)	P-value
Age, years (median, interquartile range)	57 (12)	53 (17)	0·042*
Sex			
Male	5 (56)	5 (56)	1·000
Female	4 (44)	4 (44)	
Smoker status[a]			
Current smoker	0 (0)	1 (14)	1·000
Former smoker	4 (50)	3 (43)	
Never smoker	4 (50)	3 (43)	
History of pulmonary disease prior to COVID-19	4 (44)	1 (11)	0·294
Persistent respiratory symptoms post-COVID-19	9 (100)	7 (78)	0·471
Post-COVID-19 chest CT			
Groundglass opacities only	0 (0)	7 (78)	0·042*
Groundglass opacities with interstitial thickening	5 (56)	2 (22)	
Peripheral reticulations with bronchiectasis	4 (44)	0 (0)	

K.E. Konopka et al. / EClinicalMedicine 42 (2021)

Diagnosis of fibrosis

- Imaging

  spontaneous complete resolution of the radiological fibrosis over a period of time in a lot of pt …..

- PFT
- DLCO
- Pathology
- Biomarkers

Diagnosis of fibrosis

- it is still difficult to evaluate which findings represented CT features of permanent fibrotic lung disease or CT features of slowly resolving organizing pneumonia

- sensitivity of CT for detecting histopathological fibrosis was 100% (66.4%–100%), but the specificity was only moderate 66.7% (41%–92.3%)

Ball L. *Int J Mol Sci.* 2021

CT scan

- Definitive radiologic signs of lung fibrosis include:
  - Architectural distortion
  - Traction bronchiectasis
  - Honeycombing.

- Signs such as bands, reticulation, and perilobular opacities may represent either inflammatory or fibrotic changes. These changes may be encountered in the acute phase of COVID-19 and during follow-up.

- radiological signs of fibrosis on CT
  - Not always be associated with increased collagen deposition,
  - could be reversible and that the respiratory function might improve with time after recovery.

CT scan

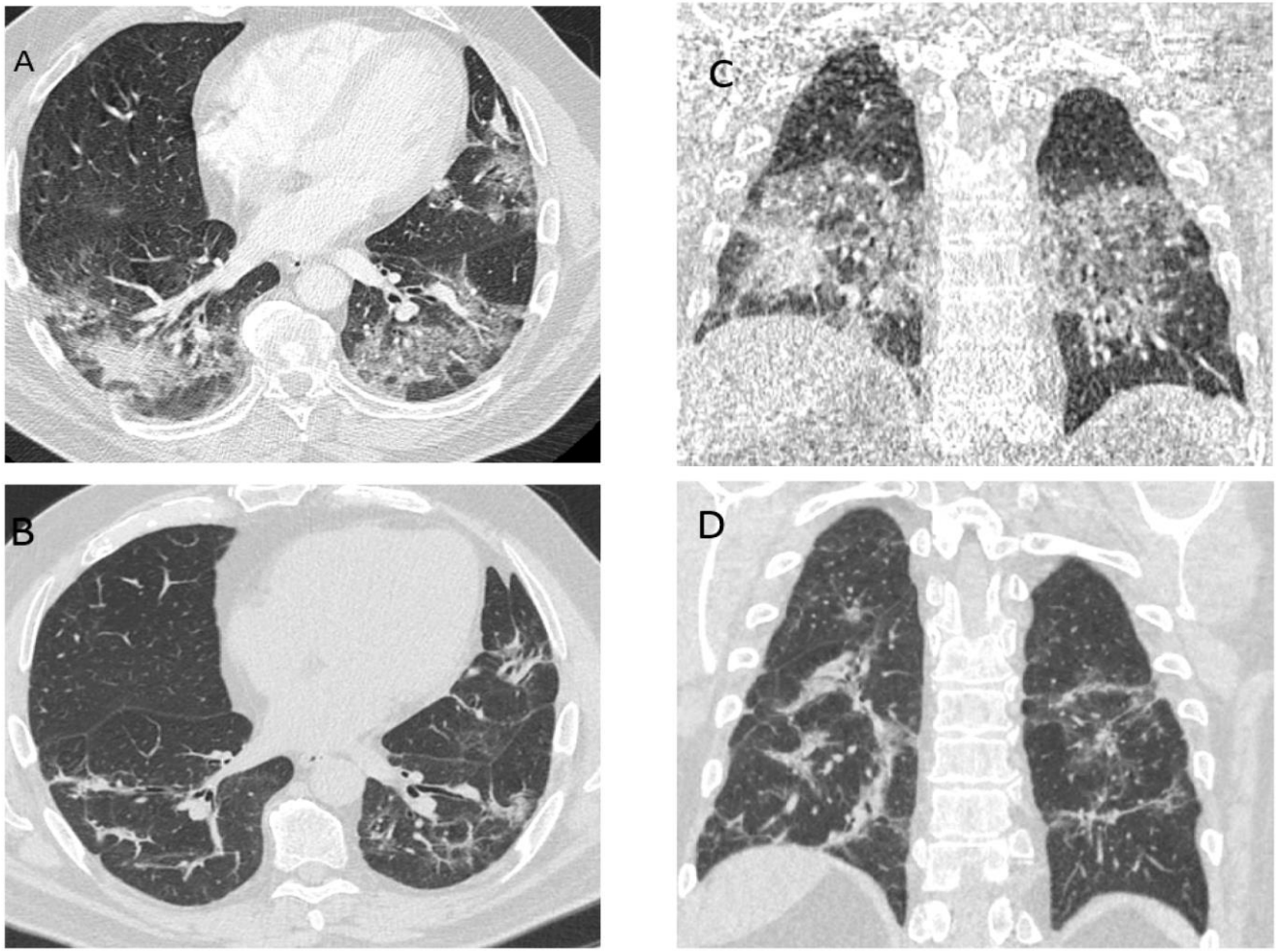
Follow-up CT scans categorize as:

- Resolution 55%
- residual non-fibrotic abnormalities : GGO , NSIP , OP 38%
- residual fibrotic abnormalities:

(subpleural reticular opacities, traction bronchiectasis, honeycombing, and signs of volume loss) 4-6%

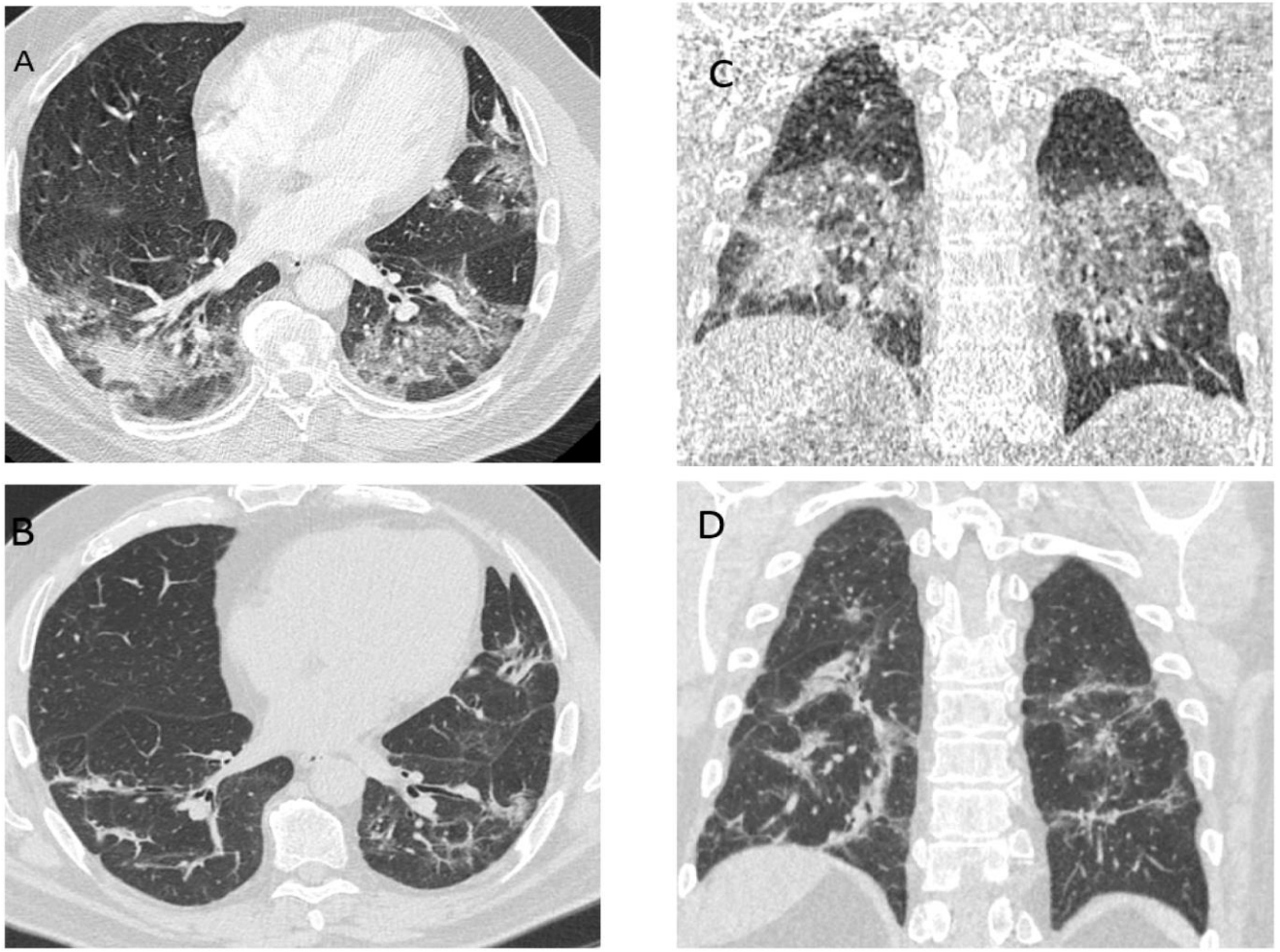
CT scan

organizing pneumonia



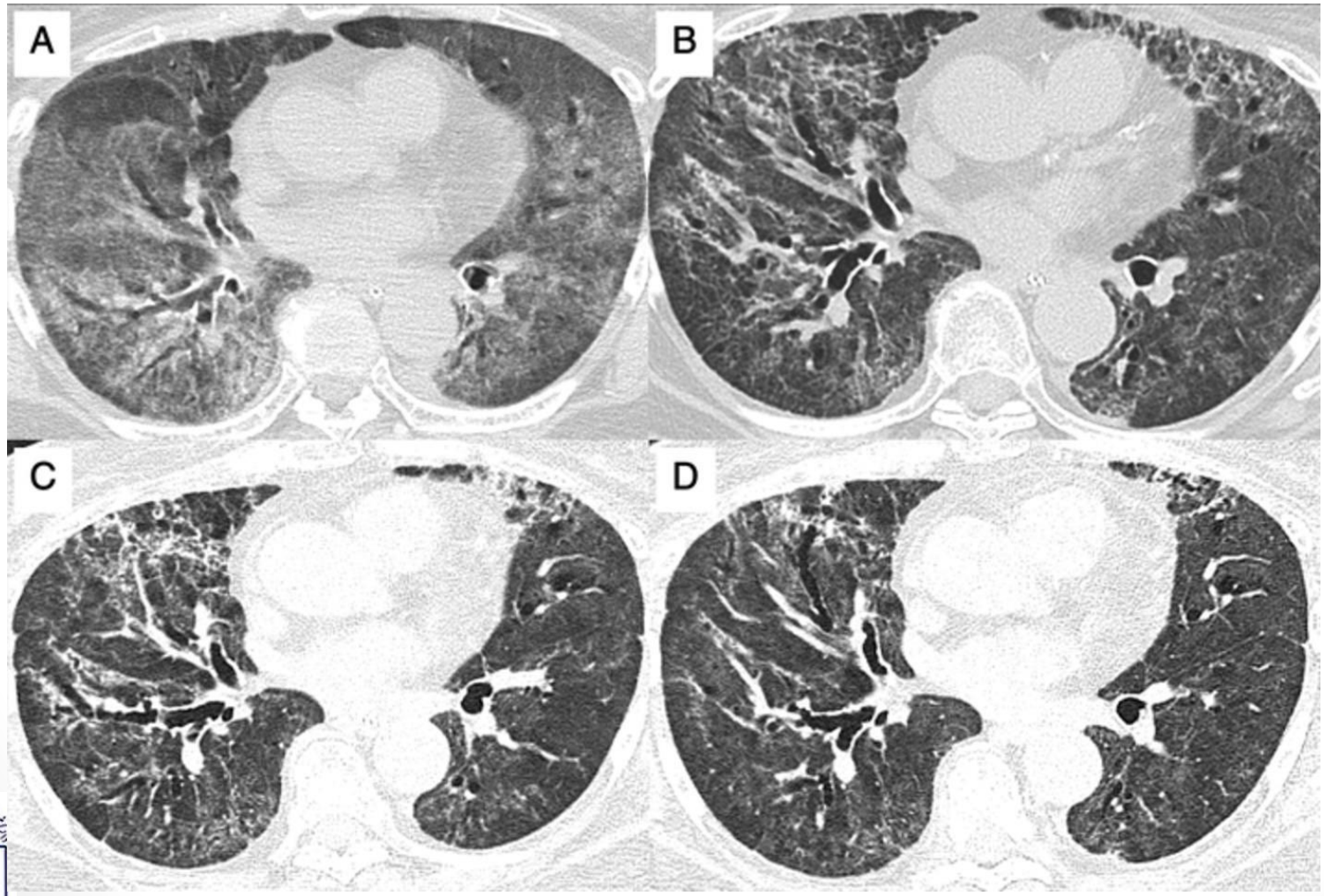
CT scan

organizing pneumonia



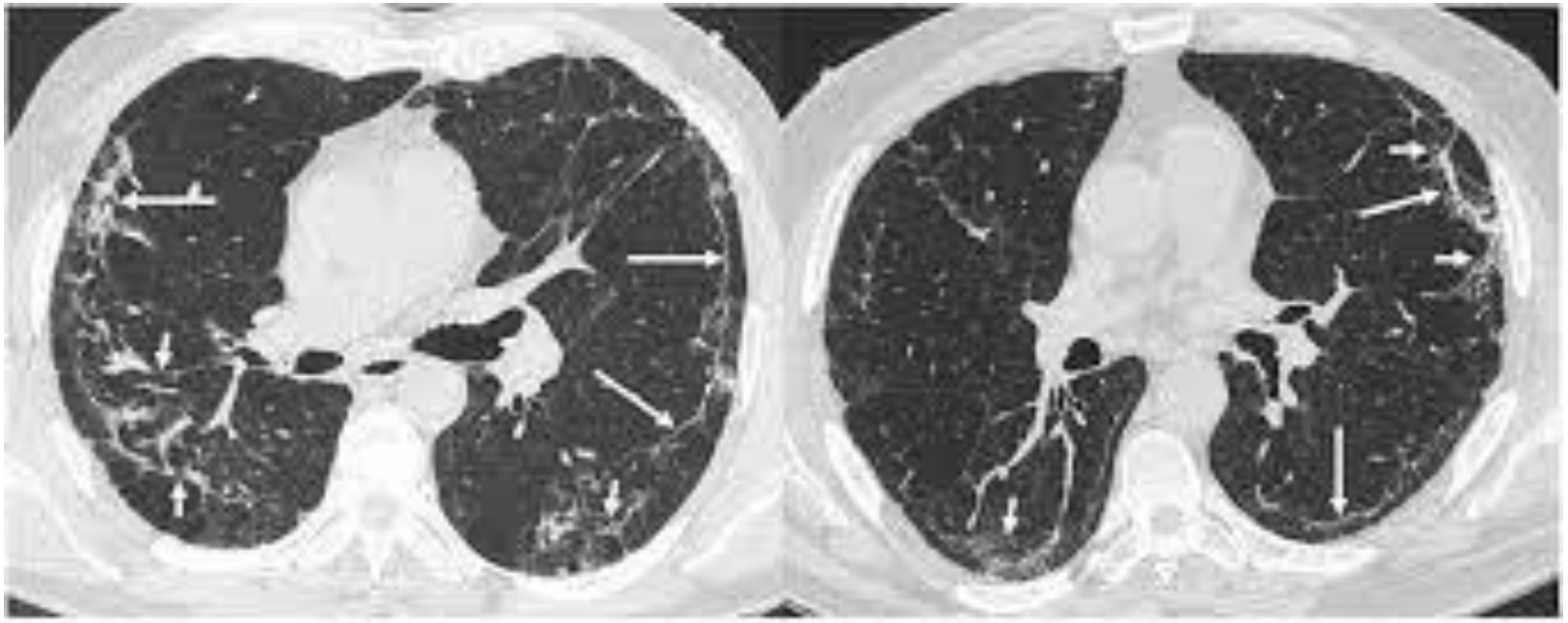
CT scan

Tractional bronchiectasis



CT scan

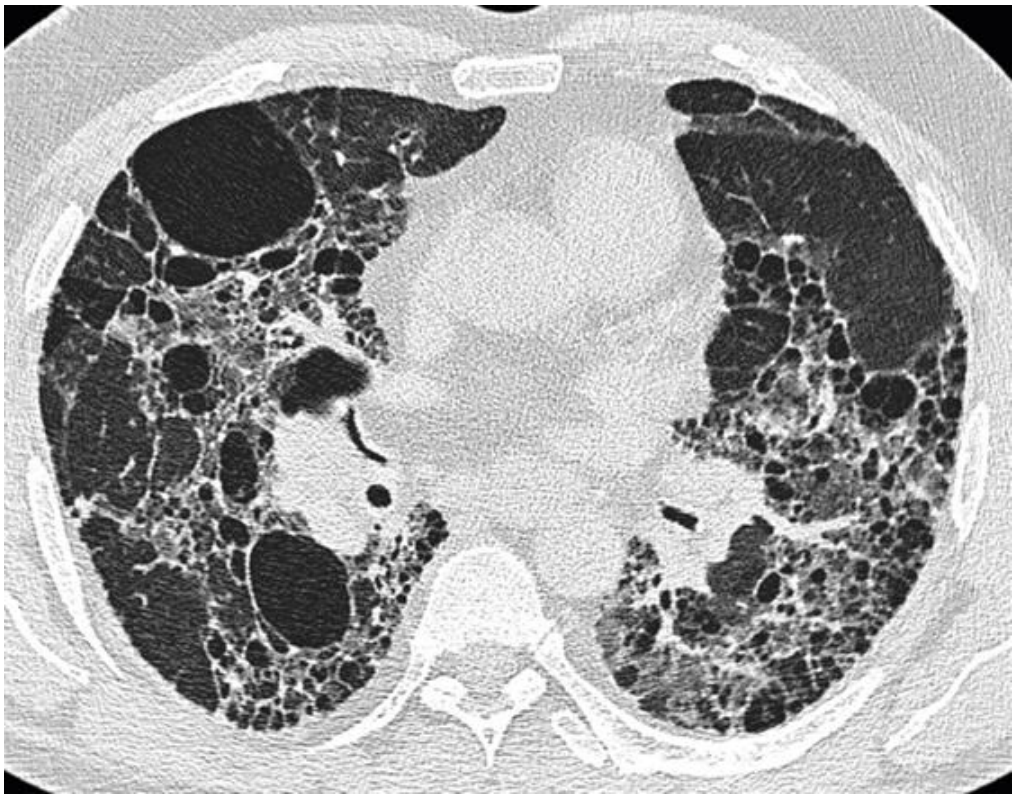
sub pleural band



Radiologia. 2021;63:258–69

CT scan

Fibrodystruction



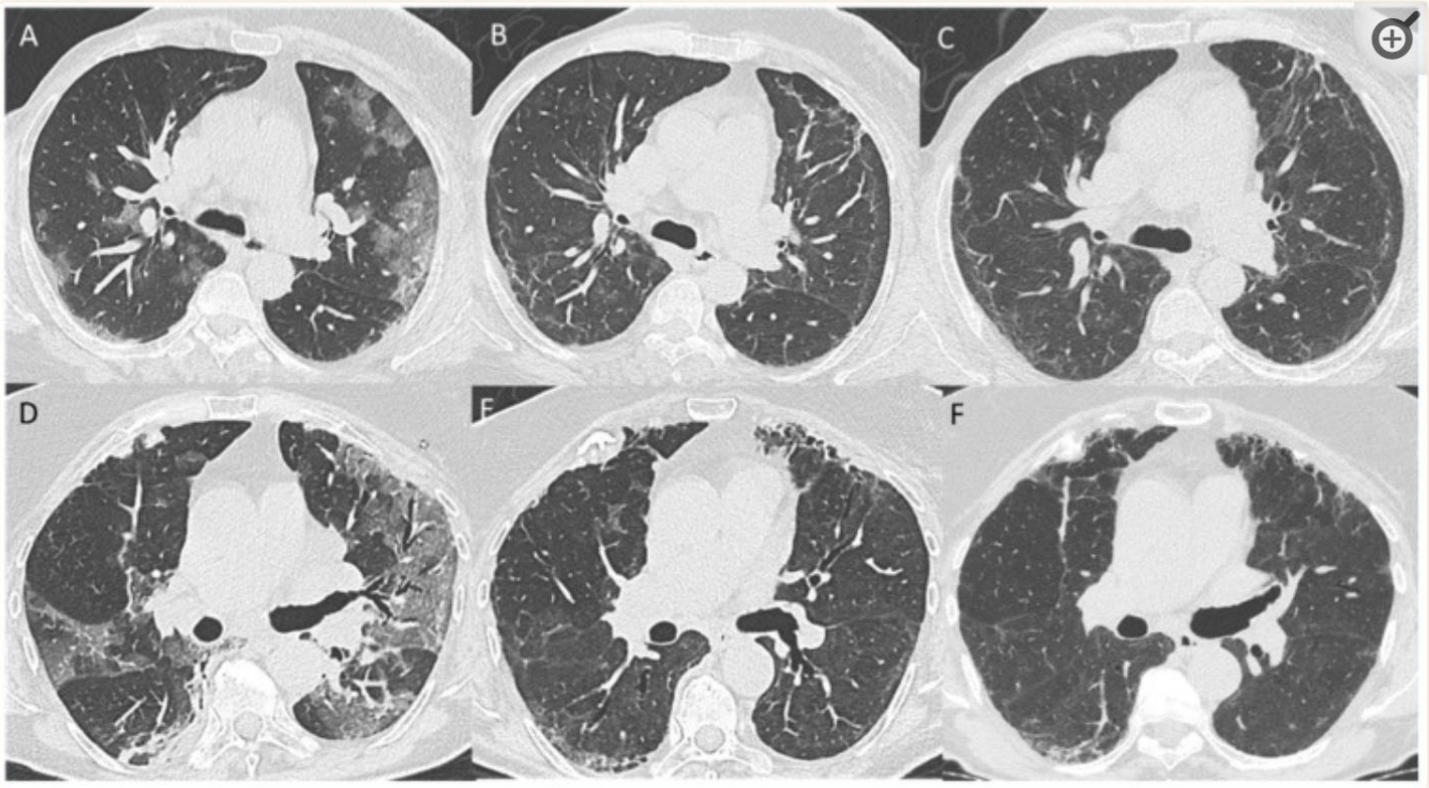


Figure 2

Baseline (**A**), 6-month follow-up (**B**), and 12-month follow-up (**C**) axial CT images showing the evolution of organizing pneumonia (OP) features towards residual non-fibrotic abnormalities resembling NSIP. Baseline (**D**), 6-month follow up (**E**), and 12-month follow-up (**F**) axial CT scans, showing patchy ground glass opacities (GGO) that are progressively replaced by reticular abnormalities and mild traction bronchiectasis resembling a fibrotic NSIP pattern.

Besutti G, Tomography. 2022 Apr 20;8(3)

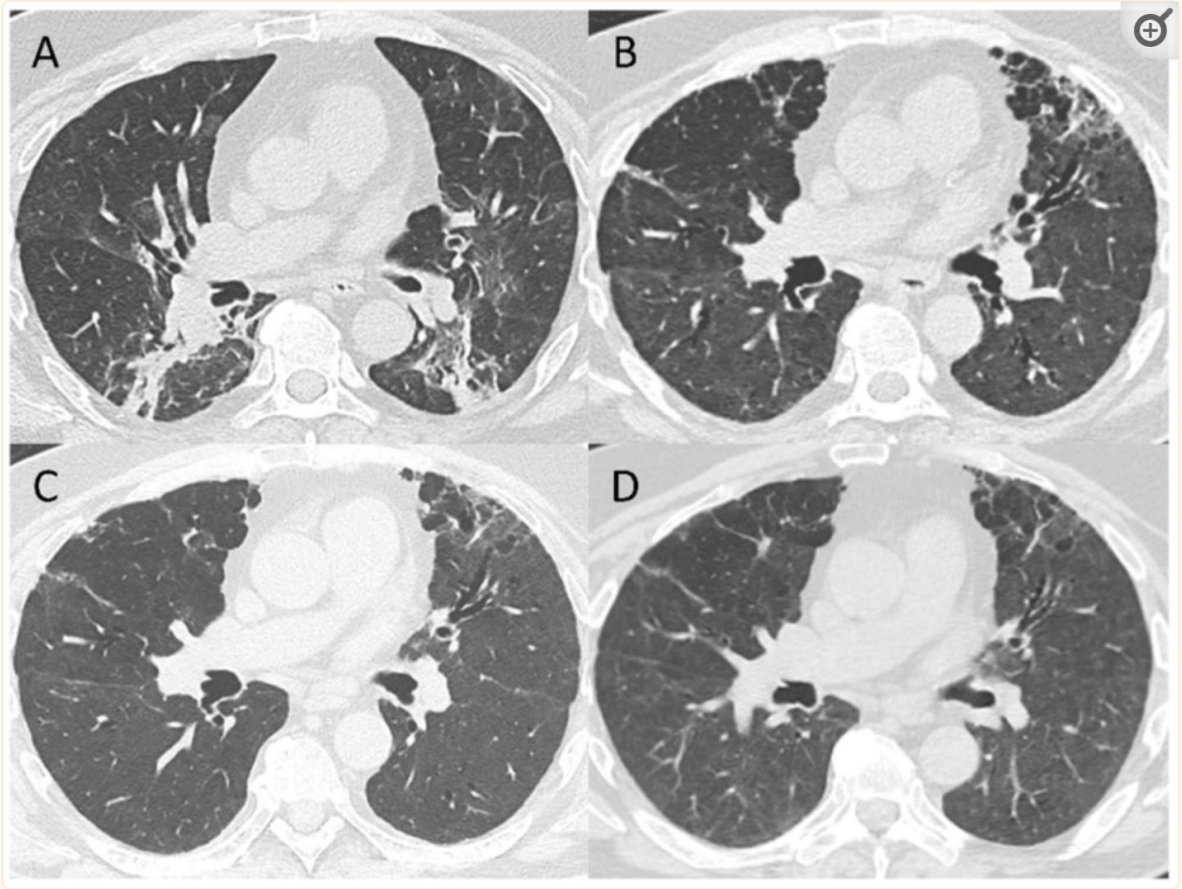


Figure 4

Representative CT images of post-ventilatory residual fibrotic abnormalities in a patient who received invasive mechanical ventilation. From baseline (**A**) to 3-month follow-up CT scan (**B**) a progressive resolution of GGO and consolidations at lower lobes can be observed, together with the appearance of bronchiectasis, GGO, and cystic spaces in the subpleural interface of the anterior part of the upper left lobe in keeping with post-ventilatory damage. These abnormalities are persistent at 6-month (**C**) and 12-month follow-up CT scans, even if a decrease in residual disease extension can be observed (**D**).

Besutti G, Tomography. 2022 Apr 20;8(3)

Prevalence

- Based on your experience, what proportion of post-COVID-19 pneumonia patients develop post COVID-19 ILD?

1. 5-10%
2. 10- 20%
3. 20- 30%
4. >30%

Prevalence

- What percentage of the lesion remains on the CT scan after 6 months?

1. 1-5 %
2. 5-10%
3. 10- 20%
4. 20- 30%
5. 30- 40%

Prevalence

- About 25% of patients who survive ARDS will manifest evidence of restrictive lung disease on pulmonary function tests (PFTs) in the next 6 months from diagnosis

- residual CT lung abnormalities in 23–72% COVID-19 survivors 6 months after the disease

- frequency of CT features suggestive of lung fibrosis have been variously reported at 3 to 6 months, ranging from 1% to 70%

Prevalence

Risk factors associated with post-COVID-19 ILD:

- Age more than 50 years
- Increasing severity of COVID-19 pneumonia
- Increased length of ICU stay
- Use of mechanical ventilation
- Smoking
- Chronic alcoholism

Sundeep S. Lung India. 2022

5-7 month follow up

Residual fibrotic abnormalities		18 (4.4%)
Global extension (%), median (IQR)		30% (20%; 39%)
Subpleural reticulations		15 (3.7%)
Bronchiectasis		16 (4.0%)
	Central	-
	Peripheral	12 (3.0%)
	Both	4 (1.0%)
	Mild	8 (2.0%)
	Moderate	8 (2.0%)
	Severe	-
Honeycombing		2 (0.5%)
Volume loss		9 (2.2%)
Ground glass opacities		14 (3.5%)
	Fibrotic NSIP	14 (3.5%)
Pattern	UIP	1 (0.2%)
	UIP probable	3 (0.7%)

Besutti G, Tomography. 2022 Apr 20;8(3)

Residual non-fibrotic abnormalities		152 (37.5%)
Global extension (%), median (IQR)		20% (10%; 30%)
Overt GGO		20 (4.9%)
Barely visible GGO		110 (27.2%)
Number of lobes involved by GGO, median (IQR)		4 (3; 5)
Parenchymal bands		11 (2.7%)
	Lobar	-
	Peripheral	11 (2.7%)
Consolidations		4 (1.0%)
	Lobar	
	Peripheral	
Perilobular opacities		32 (7.9%)
Nodules		2 (0.5%)
Bronchiectasis		52 (12.8%)
	Central	1 (0.2%)
	Peripheral	44 (10.9%)
	Both	7 (1.7%)
	OP	12 (3.0%)
Pattern	Non-fibrotic NSIP	103 (25.4%)
	Mixed	32 (7.9%)

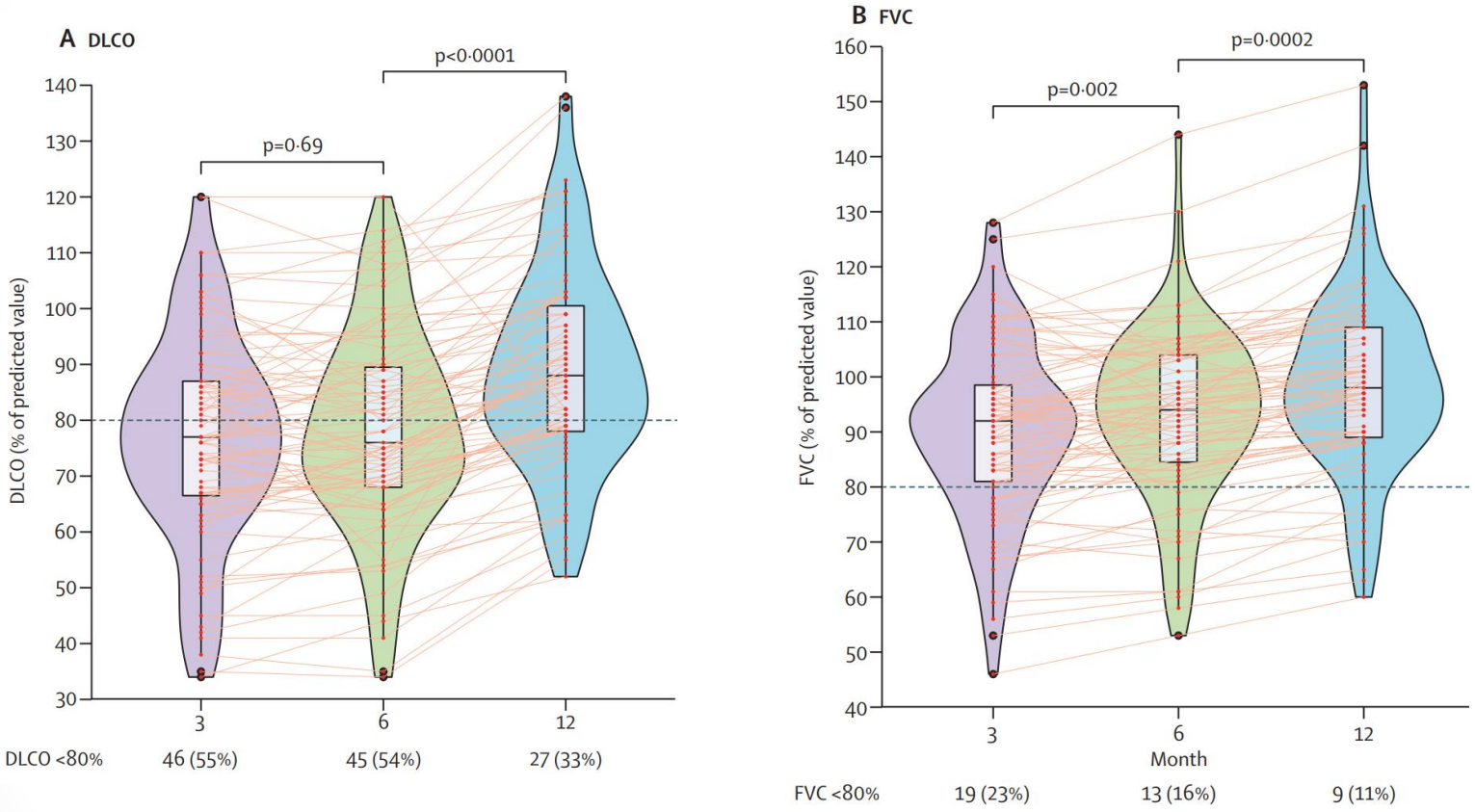
Besutti G, Tomography. 2022 Apr 20;8(3)

PFT

FEV_1	−1.2 [-1.5; −0.4]	−0.8 [-1.2; −0.2]*	0.1 [-0.7; 0.5]	0.0 [-0.5; 0.7]	**<0.001**
(z-score) ([c])					
FVC	−1.4 [-2.0; −0.9]	−1.0 [-1.7; −0.6]*	−0.3 [-0.8; −0.5]	−0.2 [-0.8; 0.5]	**<0.001**
(z-score) ([c])					
FEV_1/FVC	0.9 [0.2; 1.4]	0.6 [0.1; 1.3]	0.4 [-0.4; 0.9]	0.3 [-0.3; −0.8]	**0.009**
(z-score) ([c])					
TL_{CO}	−1.4 [-2.1; −0.7]	−1.1 [-1.9; −0.4]*	−0.4 [-1.3; 0.5]	−0.5 [-1.2; 0.4]	**<0.001**
(z-score) ([d])					
K_{CO}	0.1 [-0.7; 1.0]	0.4 [-0.7; 0.9]	0.0 [-1.1; 0.5]	−0.3 [-1.1; 0.4]	NS
(z-score) ([d])					
MIP **(z-score) ([e])**	−0.3 [-1.2; 0.5]	−0.3 [-0.9; 0.8]	0.1 [-0.9; 0.8]	−0.3 [-0.7; 0.5]	NS
MEP	−1.1 [-1.9; −0.1]	−1.0 [-1.6; −0.1]	−0.2 [-0.9; 0.7]	−0.3 [-1.1; 0.4]	**0.005**
(z-score) ([e])					
LCI (°)	1.0 [0.0; 2.2]	0.3 [-0.9; 1.8]	0.7 [-0.1; 2.2]	1.1 [-0.7; 1.7]	NS
(z-score) ([e])					
TLC	−2.7 [-3.1; −2.1]	−2.2 [-2.7; −1.5]*	−0.5 [-0.8; −0.2]	−0.5 [-0.8; 0.2]	**<0.001**
(z-score) ([e])					

Stylemans, *Respiratory medicine* vol. 182 .2021

PFT



Wu, Xiaojun *The Lancet. Respiratory medicine* vol. 9,7 (2021):

PFT

Pulmonary function, 6MWT, and chest CT scan findings in all patients at 1-year follow-up.

		Mild/moderate(n = 50)	Severe/critical(n = 40)	*P*
FVC%, (n = 90)Normal range ≥ 80%	101.17 ± 16.60	102.59 ± 14.71	99.38 ± 18.73	0.364
FEV_1% pred, (n = 90)Normal range ≥ 80%	100.85 (87.88, 108.68)	101 (88.55, 107.92)	99.7 (84.88, 110.18)	0.881
≥ 80%, N (%)	74 (82.22)	42 (84)	32 (80)	0.622
< 80%, N (%)	16 (17.78)	8 (16)	8 (20)	
FEV_1/FVC, (n = 90)Normal range ≥ 70%	79.74 (75.86, 84.23)	79.37 (75.75, 85.19)	79.94 (76.47, 83.22)	0.951
≥ 70%, N (%)	81 (90)	46 (92)	35 (87.5)	0.724
< 70%, N (%)	9 (10)	4 (8)	5 (12.5)	
		Mild/moderate(n = 35)	Severe/critical(n = 35)	*P*
TLC%, (n = 70)Normal range ≥ 80%	98.86 ± 12.24	100.34 (94.9, 108)	94.98 (87.1, 106.5)	0.079
≥ 80%, N (%)	66 (94.29)	33 (94.29)	33 (94.29)	1.000
50-80%, N (%)	4 (5.71)	2 (5.71)	2 (5.71)	
RV%, (n = 70)Normal range ≥ 65%	105.96 (93.78, 117.96)	114.2 (95.3, 124.26)	102.1 (89.6, 114.49)	0.113
DLCO%, (n = 70)Normal range ≥ 80%	99.50 ± 18.82	99.54 ± 21.62	99.46 ± 15.84	0.856
≥ 80%, N (%)	60 (85.71)	28 (80)	32 (91.43)	0.172
60-80%, N (%)	10 (14.29)	7 (20)	3 (8.57)	

Zhao, Yumiao *International journal of infectious diseases* , vol. 112 (2021)

Treatment

- Anti-inflammatory and Anti fibrotic for :

- Prevention

- treatment

Treatment

Review > Lancet Respir Med. 2020 Aug;8(8):807-815. doi: 10.1016/S2213-2600(20)30225-3. Epub 2020 May 15.

Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy

Peter M George [1], Athol U Wells [1], R Gisli Jenkins [2]

Affiliations + expand

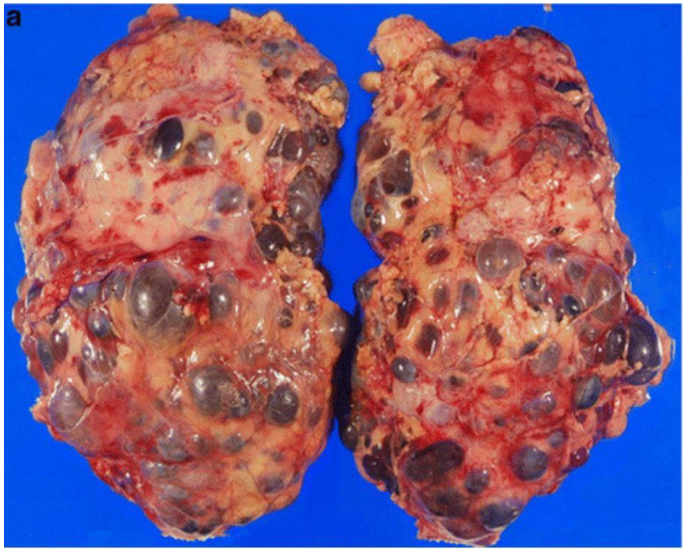
PMID: 32422178 PMCID: PMC7228727 DOI: 10.1016/S2213-2600(20)30225-3

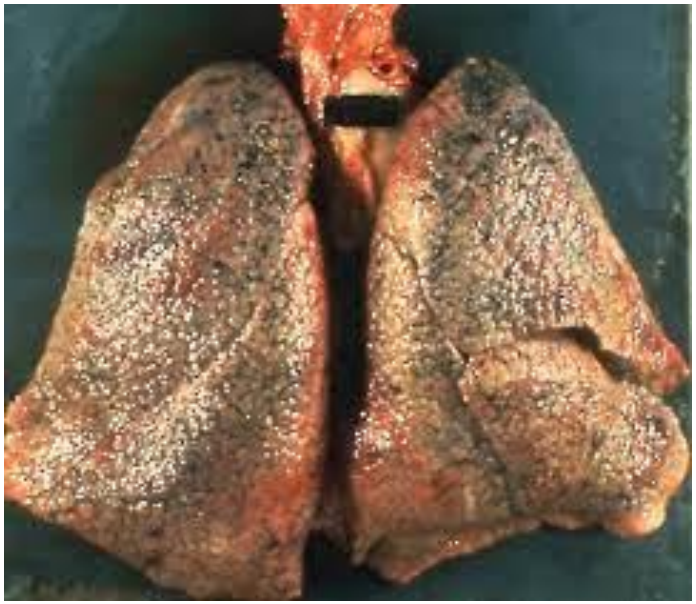
Free PMC article

Abstract

In December, 2019, reports emerged from Wuhan, China, of a severe acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the end of April, 2020, over 3 million people had been confirmed infected, with over 1 million in the USA alone, and over 215 000 deaths. The symptoms associated with COVID-19 are diverse, ranging from mild upper respiratory tract symptoms to severe acute respiratory distress syndrome. The major risk factors for severe COVID-19 are shared with idiopathic pulmonary fibrosis (IPF), namely increasing age, male sex, and comorbidities such as hypertension and diabetes. However, the role of antifibrotic therapy in patients

Fibrosis





Treatment

- Some of the newly studied antifibrotic drugs target different molecules of the TGF-β pathway including
  - αvβ6 integrin
  - PLN-74809
  - Galectins

- Recent experimental data support the potential mechanism of these novel drugs in preventing the COVID-19 infection, based on the structure of SARS-CoV-2 spike proteins, particularly the Arg-Gly-Asp integrin-binding domain and the N-terminal galectin fold

Treatment

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Infect Dis Poverty. 2021; 10: 31.
Published online 2021 Mar 18. doi: 10.1186/s40249-021-00813-8
PMCID: PMC7969149
PMID: 33731163

Efficacy of the combination of modern medicine and traditional Chinese medicine in pulmonary fibrosis arising as a sequelae in convalescent COVID-19 patients: a randomized multicenter trial

Zhen-Hui Lu,[#1] Chun-Li Yang,[#2] Gai-Ge Yang,[3] Wen-Xu Pan,[4] Li-Guang Tian,[5,6] Jin-Xin Zheng,[5,6] Shan Lv,[5,6] Shao-Yan Zhang,[1] Pei-Yong Zheng,[✉1] and Shun-Xian Zhang[✉5,6]

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Infect Dis Poverty

Treatment

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Rural treatment of COVID-19 patients with pirfenidone, nitazoxanide and colchicine. Case series

Brandon Iturbe Esquivel [1], José Meneses Calderón [2], Luis Edgar Concepción Carrillo [3], Hugo Mendieta Zeron [4]

Affiliations + expand

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Free article

Abstract

Combined treatments against SARS-CoV-2 are emerging and some have taken into account the post-COVID-19 fibrosis. The aim of this survey was to report the experience of treating COVID-19 patients with pirfenidone, nitazoxanide (NTZ) and colchicine. It was a case series report of COVID-19 patients treated from December 2020 to March 2021, in a rural health center located in the State of Mexico,

Treatment

- Pirfenidone inhibits TGF-β-induced fibronectin synthesis and has antifibrotic and antiinflammatory properties,

- Nintedanib
- Approved by FDA for IPF treatment
- Inhibiting the cascades of fibroblasts and myofibroblasts
- reduces the decline of FVC in IPF
- Benefits seen by four to six weeks.

- SENCIS trial, has shown that subjects with systemic sclerosis-associated ILD (SSc-ILD) have a clinically relevant benefit on the progression.

- Both drugs, approved in by the FDA in 2014, have different mechanisms of action that attenuate the rate of lung function decrease and enhance life expectancy

Table 1. Clinical trials of drugs for the treatment of post-COVID lung fibrosis.

Treatment	NCT Number		Phase	Number Enrolled	Study Design
Nintedanib	NCT04338802	[34]	II	96	Single-center, randomized, placebo-controlled 150 mg POBID for 8 weeks
	NCT04541680	[35]	III	250	Single-center, randomized, placebo-controlled 150 mg POBID for 12 months
	NCT04619680	[36]	IV	120	Multicenter, randomized, placebo-controlled 150 mg POBID for 180 days
Pirfenidone	NCT04282902	[37]	III	294	Single-center, randomized, placebo-controlled 2 × 267 mg POTID for 4 weeks
	NCT04607928	[38]	II	148	Multicenter, randomized, placebo-controlled 2 × 267 mg POTID, 7 days after 4 × 267 mg TID for 24 weeks
Treamid	NCT04527354	[39]	II	60	Multicenter, randomized, placebo-controlled study 50 mg daily PO for 4 weeks
LYT-100	NCT04652518	[40]	II	168	Multicenter, randomized, placebo-controlled PO BID for 91 days
Collagen-Polyvinylpyrrolidone	NCT04517162	[41]	I	90	Single-center, randomized, placebo-controlled 1.5 mL IM BID for 3 days, then 1.5 mL QD for 4 days
Prednisone	NCT04551781	[42]	–	450	Single-center, randomized, placebo-controlled 20 mg daily for 14 IM
Bovhyaluronidase azoximer	NCT04645368	[43]	–	160	Multicenter, randomized, placebo-controlled 3000 ME IM once in 5 days for 15 IM
BIO 300 (genistein)	NCT04482595	[44]	II	66	Single-center, randomized, placebo-controlled 1500 mg daily PO for 12 weeks
Tetrandrine	NCT04308317	[45]	IV	60	Single-center, randomized, compared to standard therapy 60 mg daily PO for a week
Fuzheng Huayu Tablet	NCT04279197	[46]	II	160	Single-center, randomized, placebo-controlled 1.6 g TID PO for 24 weeks
Anluohuaxian					Multicenter, randomized, compared to ndard therapy PO for 3 months
Stromal Vascular Fraction					nter, randomized, bo-controlled s, No data for injection requency
IN01Vaccine					N01 is injected on days 28, 42, and 56, stage, vaccination is ery 2 months with the e and regimen as during introduction, compared to the patients receiving standard therapy

There is not any evidance

Review .....

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Role of antifibrotic drugs in the management of post-COVID-19 interstitial lung disease: A review of literature and report from an expert working group

Sundeep Santosh Salvi,[1] Deesha Ghorpade,[1] Sahajal Dhoori,[2] Raja Dhar,[3] Harjit Dumra,[4] Prashant N Chhajed,[5] Parathasarathi Bhattacharya,[6] Sujeet Rajan,[7] Deepak Talwar,[8] Devasahayam J Christopher,[9] Murali Mohan,[10] and Zarir Udwadia[11]

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This article has been corrected. See Lung India. 2022; 39(3): 310.

Challenge …

- Between Pirfenidone and Nintedanib, which antifibrotic drug are you more likely to use?
- At what point of time are you likely to start them?
- What should be the duration of antifibrotic drugs for the management of post-COVID-19 ILD?

Practice

Suitable for anti fibrotic:

1. Symptomatic
2. Presence of traction bronchiectasis, honecombing and distorted lung architecture on HRCT
3. Requiring oxygen after 4 weeks

Not Suitable for anti fibrotic :

1. Symptomatic patients not requiring oxygen
2. a lone high CT radiology score .

might be candidates for anti fibrotic drugs.

- Progressive decrease of lung function
- worsening radiological signs of fibrosis

- If you agree to use antifibrotic drugs for post-COVID ILD, at what point of time are you likely to start them?

Practice

➢ *Do patients need to be screened for ILD?*

- Clinical evaluation
- PFT
- 6MWT
- Imaging

Alternative Treatment

- Lung transplant
- Pulmonary Rehabilitation

Transplant

- multicenter study of successful lung transplant procedures in 11 out of 12 critically ill COVID-19 patients who had not recovered even after proper medical management and were at high risk of dying.
- On the 30th-day post-surgery, 100% of the patients were alive
- 11 out of 12 remained alive and recovering well after a median follow-up of 80 days (32-160)
- They suggested a transplantation decision for patients :
  - who would probably not survive
  - younger than 65 years old
  - no pre-existing comorbidities or manageable comorbidities

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pulmonary rehab.

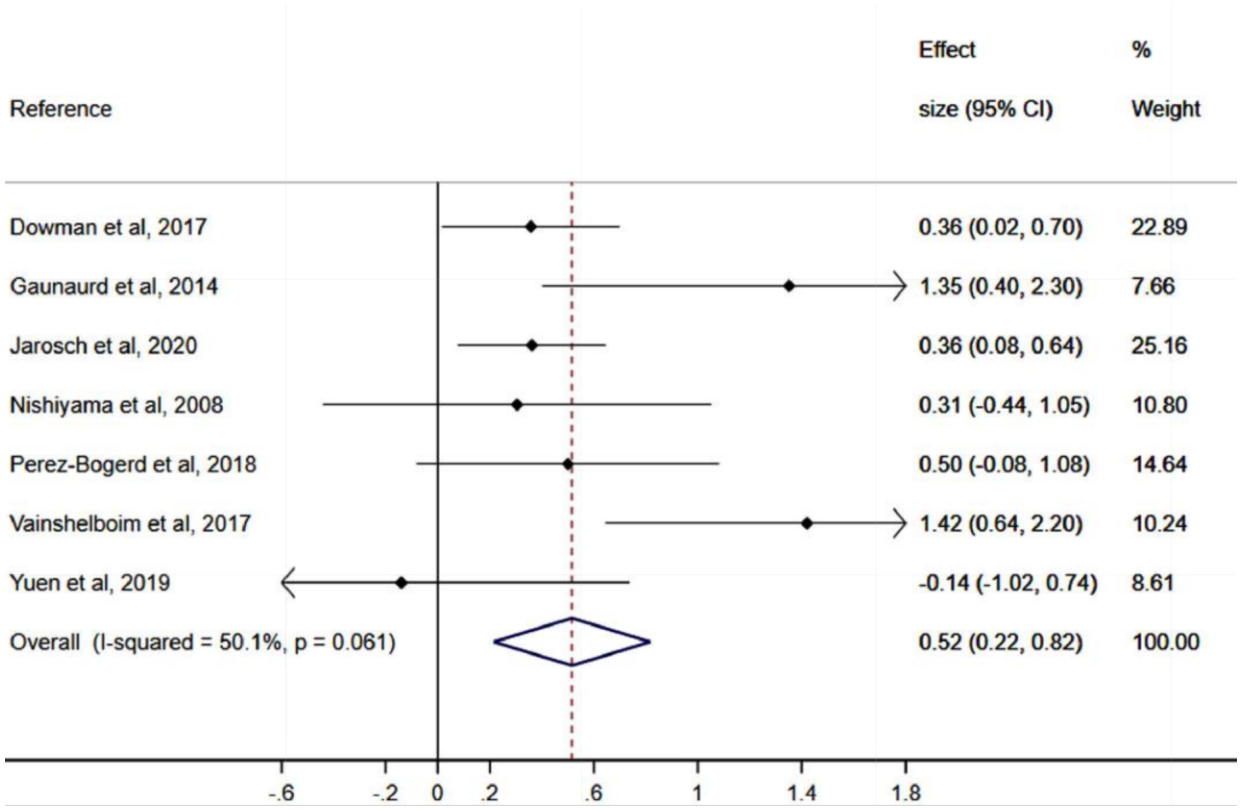
- pulmonary rehabilitation could improve physical and psychological conditions, including exercise training, education, and behavioral changes




Arch Phys Med Rehabil. 2021 ; systemathic reviewe

pulmonary rehab.

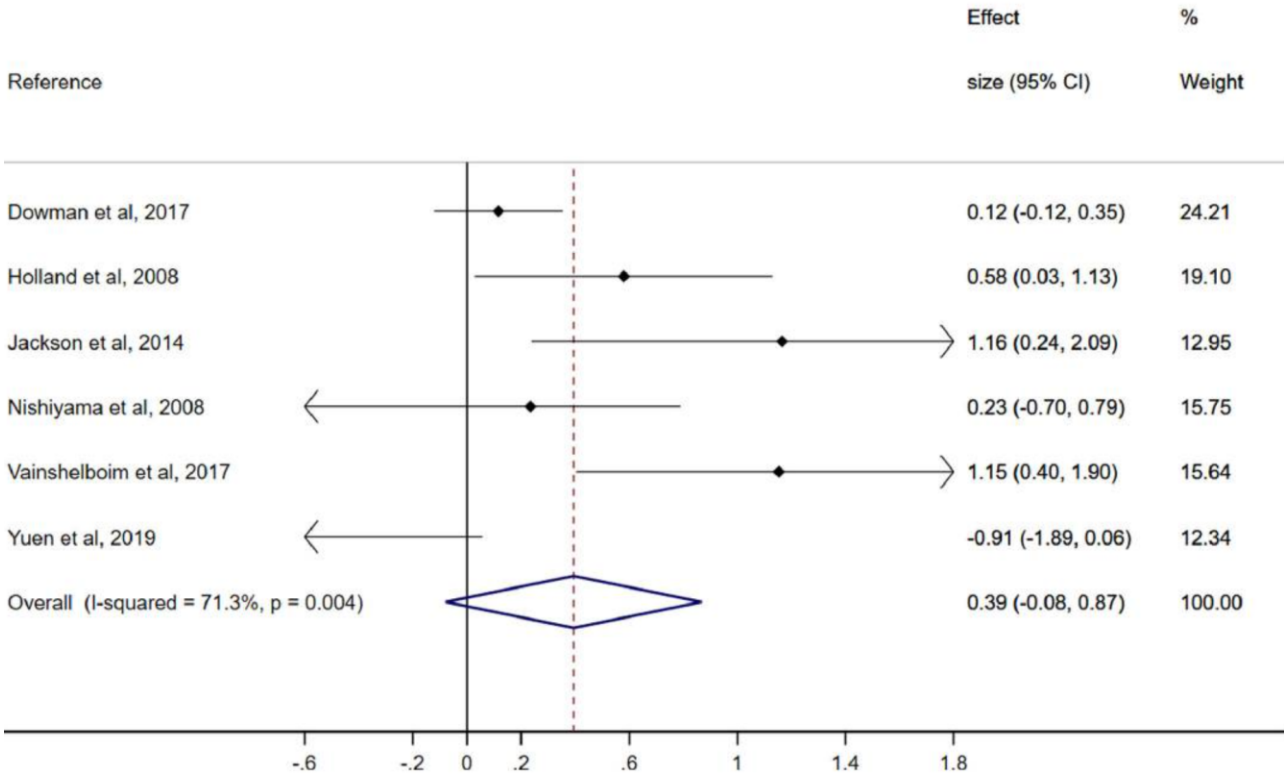
Effect of PR vs usual care on health related quality of life after intervention



Reina-Gutiérrez, A Systematic Review and Meta-analysis. *Archives of physical medicine and rehabilitation* 2021.03.035

pulmonary rehab.

Effect of PR vs usual care on dyspnea life after intervention



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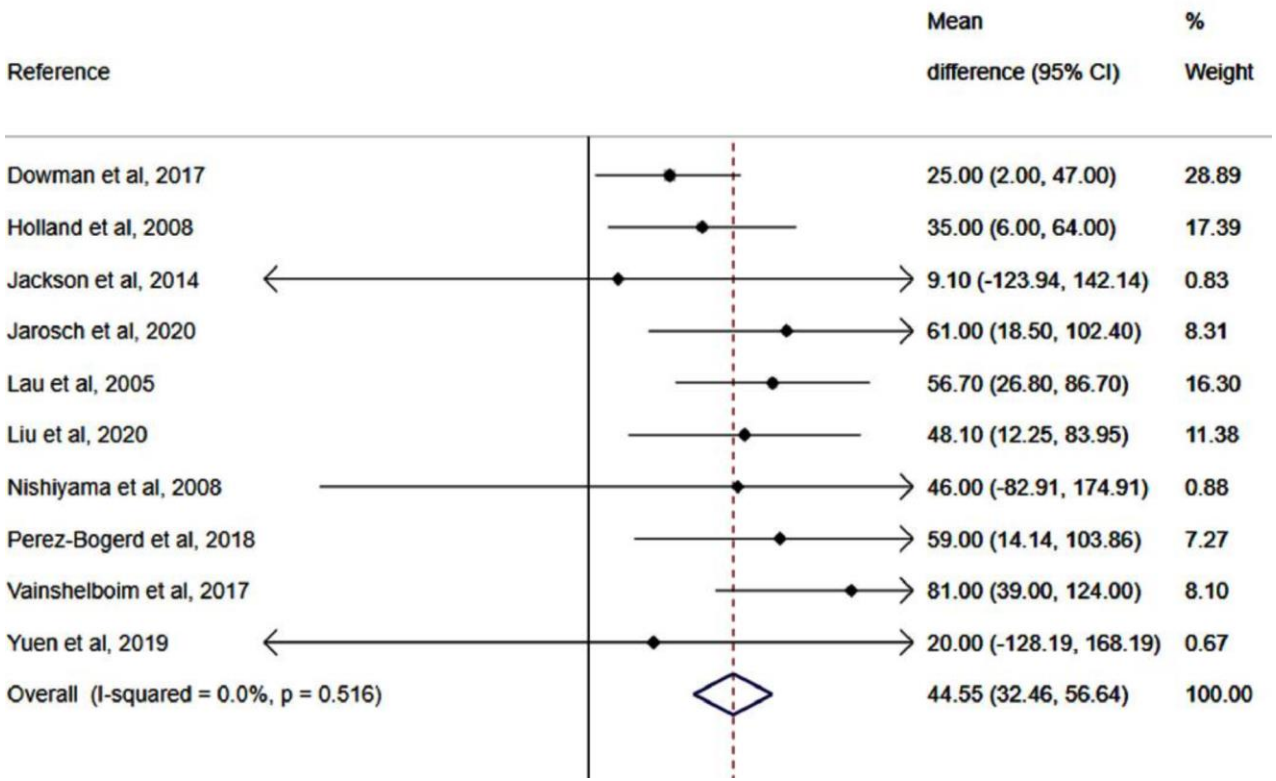
pulmonary rehab.

Effect of PR vs usual care on exercise capacity after intervention



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