POST COVID-19 FIBROZA PLUĆA

SPECIJALISTIČKI SEMINAR – BOLESTI PLUĆNOG INTERSTICIJUMA

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spec.pulmolog; subspec. intenzivne medicine

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CILJEVI

- Definicija
- Potencijalni uzroci
- Faktori rizika za nastanak ILD/PF
- Strategija menadžementa definirane bolesti
- Osvrt na kliničke studije koje istražuju prirodan tok i potencijalne terapeutske učinke

COVID-19 STATISTIKA...

- Broj oboljelih u svijetu: 262.350.409
- Broj umrlih u svijetu: 5.211.429

- Broj zaraženih osoba u SAD: 48.441.328
- Broj umrlih u SAD: 778.667

- Broj rehospitalizacija i stopa smrtnosti iznosila je 27% unutar 60 dana od dehospitalizacije preživjelih pacijenata prema podacima Veteranske bolnice u USA

JAMA 2021; 325(3) 304-306

POST COVID-19 PLUĆNE KOMPLIKACIJE

- Perzistentni simptomi: *kašalj, dispnea, bol ili stezanje u grudima*
- Rezultati ispitivanja plućnih funkcija: *snižen VC, TLC, DLCo, spO2*
- Bolesti *malih disajnih puteva* i *zarobljavanje zraka*, emfizem (COPD)
- Snižene vrijednosti *6MWT*
- Abnormalni rezultati radioloških pretraga: grudni radiogram, CT scan, CTA, V/Q scan pluća
- Prevalenca PAH 8% i RV dilatacije u 10% pacijenata, dva mjeseca nakon infekcije- (J.Clin. Med. 2021 10;199)
- Plućna vaskularna bolest (tromboza, infarkti, embolus)
- Intersticijske bolesti pluća (ILD)

RSNA

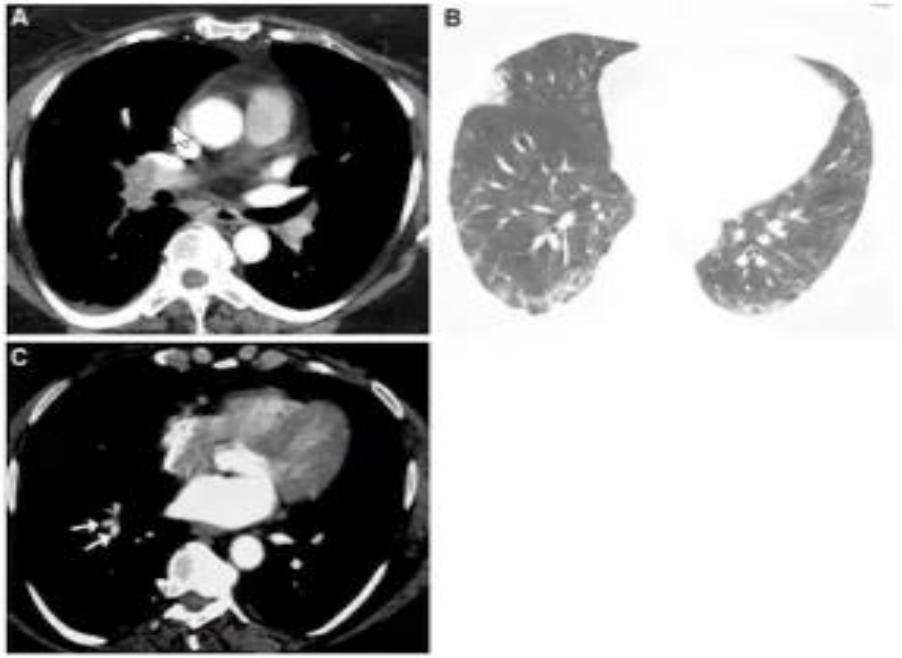


Figure 5: Images depict pulmonary vascular disease after COVID-19 in a 63-year-old woman with persistent shortness of breath and elevated d-dimer level. **(A)** Axial CT pulmonary arteriogram with persistent shortness of breath and elevated d-dimer level, 7 weeks after onset of infection, shows obstructive thrombus in right interlobar pulmonary artery. **(B)** Axial CT with lung windows at lower level shows patchy ground-glass opacity and focal wedge-shaped consolidative abnormality in right middle lobe, typical for pulmonary infarct. **(C)** Three months later, large central thrombus had resolved, but nonocclusive linear webs were present in segmental vessels (arrows), typical for chronic thromboembolic disease.

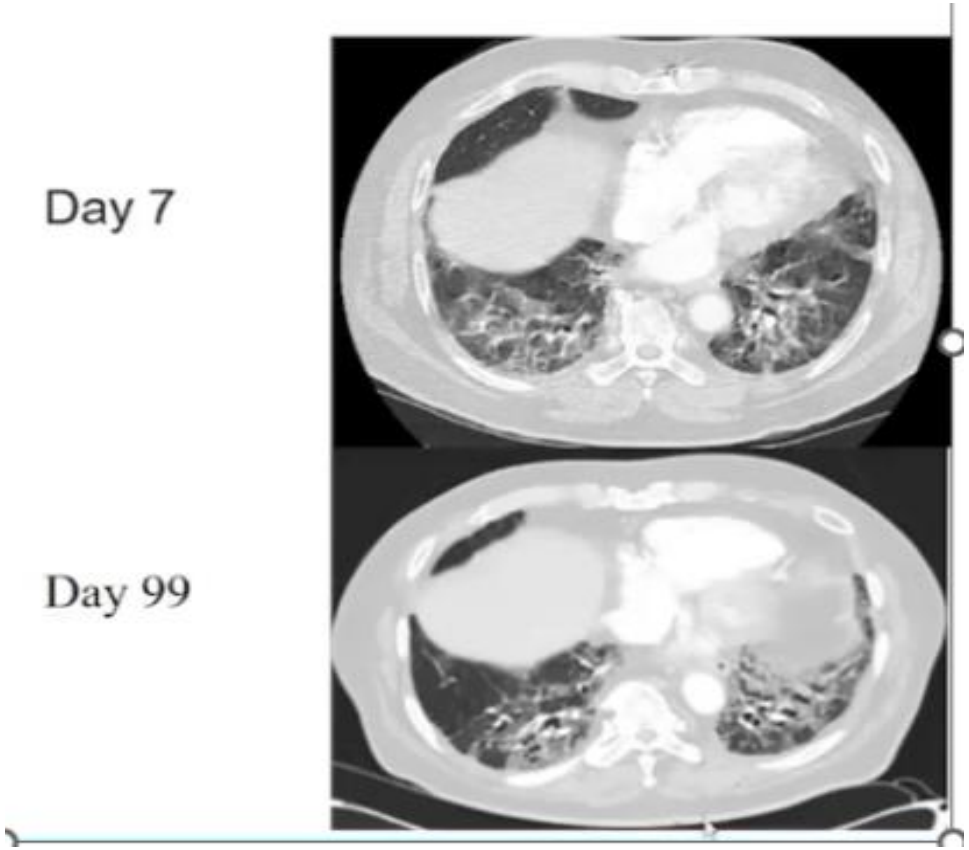
Solomon JJ. Published Online: August 10, 2021
https://doi.org/10.1148/radiol.2021211396

Radiology

Parenhimske komplikacije COVID-19

Pitanja:

1. Da li se može verificirati intersticijska bolest pluća (ILD)?
2. Da li se može verificirati plućna fibroza (PF)?
3. Da li će ovakav snimak uticati na kvalitet života pacijenta?



Radiološke i funkcionalne plućne sekvele COVID-19

- Rezidualne abnormalnosti na CT: 55.7%
  "Ground glass opaciteti" (GGO): 44.1%
  Parenhimske ili fibrozne trake: 34.8%

- Abnormalnosti plućnog funkcionalnog testiranja: 44.3%
  Restriktivne plućne bolesti: 16.4%
  Opstruktivne plućne bolesti: 7.7%

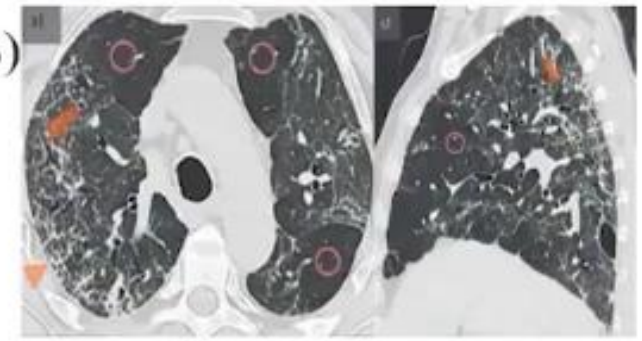
So M, et al. Radiological and functional lung sequelae of COVID-19: a systematic review and meta-analysis. BMC Pulm Med. 2021 Mar 22;21(1):97.

The Swiss COVID-19 Lung Study

- Four months following acute COVID infection:
- -Severe/critical acute COVID was associated with lower TLC, FVC, FEV_1, and D_{LCO}% pred -P_{aO2}, 6MWD, nadir SpO2, degree of desaturation during 6MWT were significantly lower

- Radiological
  -Hypoattenuated areas (66% vs 13%)
  -Reticulations (59% vs 13%)
  -Architectural distortion (52% vs 13%)

Guler SA, et al. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. Eur Respir J. 2021 Apr 29;57(4)



POST COVID-19 KOMPLIKACIJE

Restriktivna bolest pluća kao i ostale *intersticijske bolesti pluća* su evidentirane kod ambulantnih pacijenata sa blagim kliničkim oblikom bolesti
(Dadhwal i sar. 2021 Cureus 13(1):e12501)

Kohortna studija rezultata CT-a torakalnih organa ukazala je na prisustvo "*ground glass opaciteta*" u rezoluciji i novih znakova plućne fibroze

PFT su ukazali na "*restriktivni pattern"* plućne bolesti

POST COVID-19 PLUĆNA FIBROZA (PCPF)

- Ne-idiopatska forma fibroze pluća je evidentirana kod pacijenata koji su inficirani sa COVID-19
- Klinički, radiografski i/ili patološki nalaz potreban kod prethodno verificiranih ili sumnjivih slučajeva sa COVID-19 infekcijom

- Heterogen entitet
- Može se desiti tokom hospitalizacije, ali i verificirati tokom dugotrajnog praćenja
- Ne postoje zvanični podaci za frekventnost i težinu oboljenja

Ambardar, Shiva Rattan et al. "Post-COVID-19 Pulmonary Fibrosis: Novel Sequelae of the Current Pandemic." *Journal of clinical medicine* vol. 10,11 2452. 1 Jun. 2021, doi:10.3390/jcm10112452

(PCPF)- Potencijalni patogeni mehanizmi

- Virusni pneumonitis
- Endoteliolitis i hiperkoagulabilnost
- Disregulacija imunog sistema
- Proinflamatorno stanje (Citokinska oluja)
- Ekstracelularne mreže neutrofila (“NET”)- fibroza i tromboza
- Tromboembolijska bolest
- Hiperoksija i hipoksija
- ARDS
- Barotrauma i VILI (“Ventilation induced lung injury”)
- P-SILI – “Patient self-induced lung injury”
- Genetska predispozicija

Faktori rizika za post COVID-19 fibrozne promjene

Thorax. 2021 Dec;76(12):1242-1245. doi: 10.1136/thoraxjnl-2021-217031. Epub 2021 Apr 29.

Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length

Claire F McGroder [1], David Zhang [1], Mohammad A Choudhury [1], Mary M Salvatore [2], Belinda M D'Souza [2], Eric A Hoffman [3], Ying Wei [4], Matthew R Baldwin [1], Christine Kim Garcia [5 6]

Affiliations + expand

PMID: 33927016 PMCID: PMC8103561 DOI: 10.1136/thoraxjnl-2021-217031

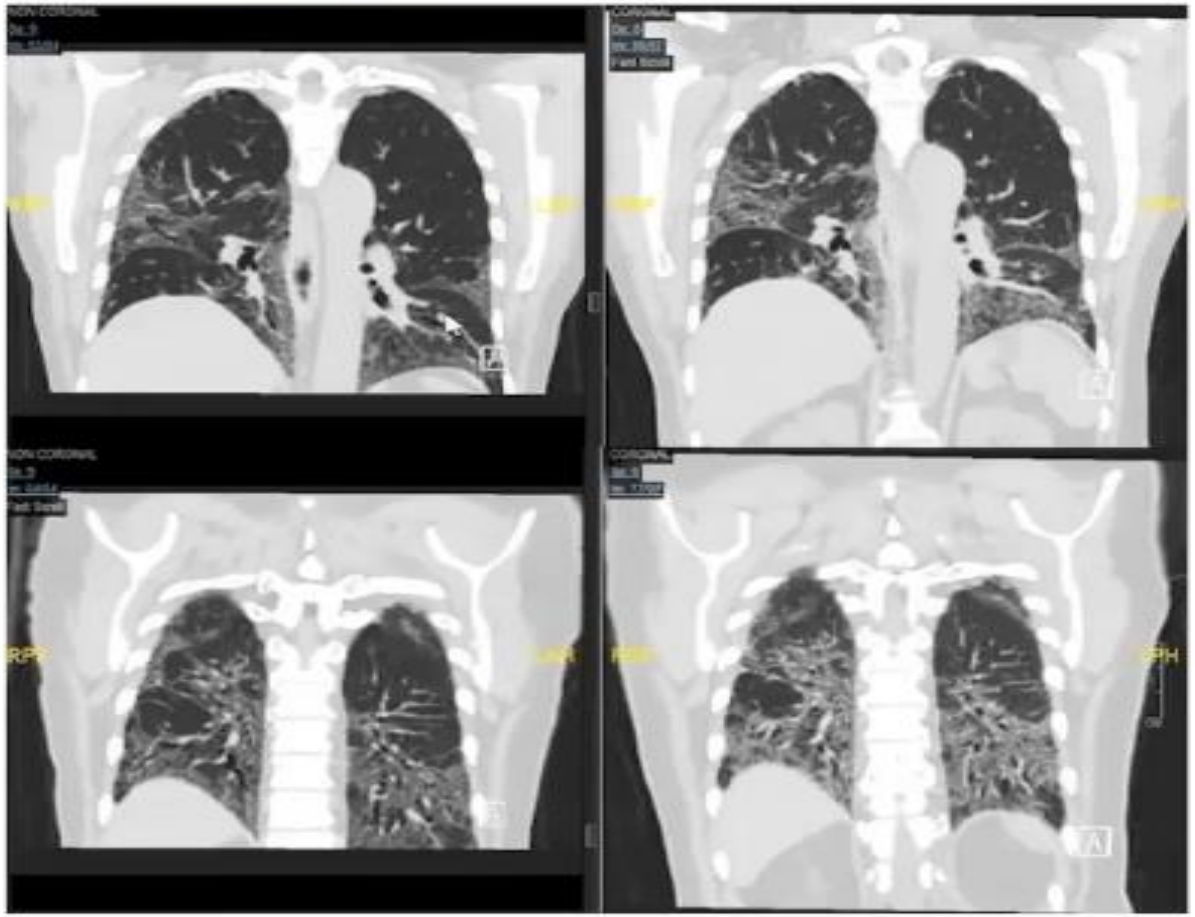
Prospektivna "single-center" studija;

- 72 pacijenta koji zahtijevaju O2 potporu praćeni su četiri mjeseca
- 32 (49%) pacijenata je zahtijevalo MV
- *Radiološke značajke*: GGO 43%, retikulacije 39%, trakcione bronhiektazije 28%
- *PFT*: 40 (53%) su imali snižen DLCO, 78% je imalo snižen 6MWT

A

CT Scan Day 0

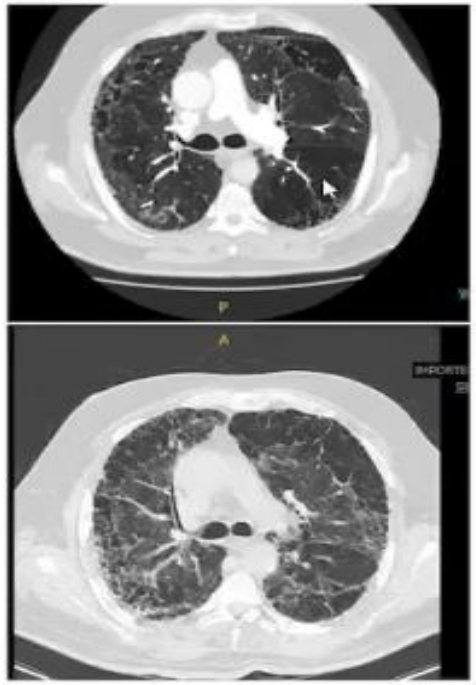
CT Scan Day 180

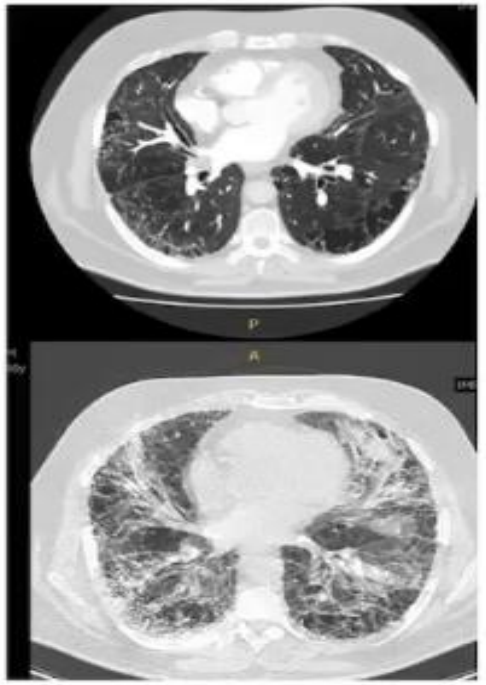


FVC (ml)
2030

FVC (ml)
1820

Post COVID Pneumonia: Obstructive lung disease





6/21/21
FEV1/FVC
: 65%
DLCO:
35%

12/11/20

Šta ne znamo????

- Koja je prevalenca post-covid fibroze
- Kako fenotipizirati pacijente da bismo odredili ko će razviti fibrozu
- Da li je post-covid fibroza progresivna bolest?
- Da li antifibrozni lijekovi umanjuju opadanje plućne funkcije kod pacijentata sa post covid fibrozom
- Da li pacijenti sa rezidualnim fibroznim promjenama imaju rizik od razvoja intersticijske plućne bolesti/fibroze u budućnosti

Faktori rizika za post COVID-19 plućnu fibrozu

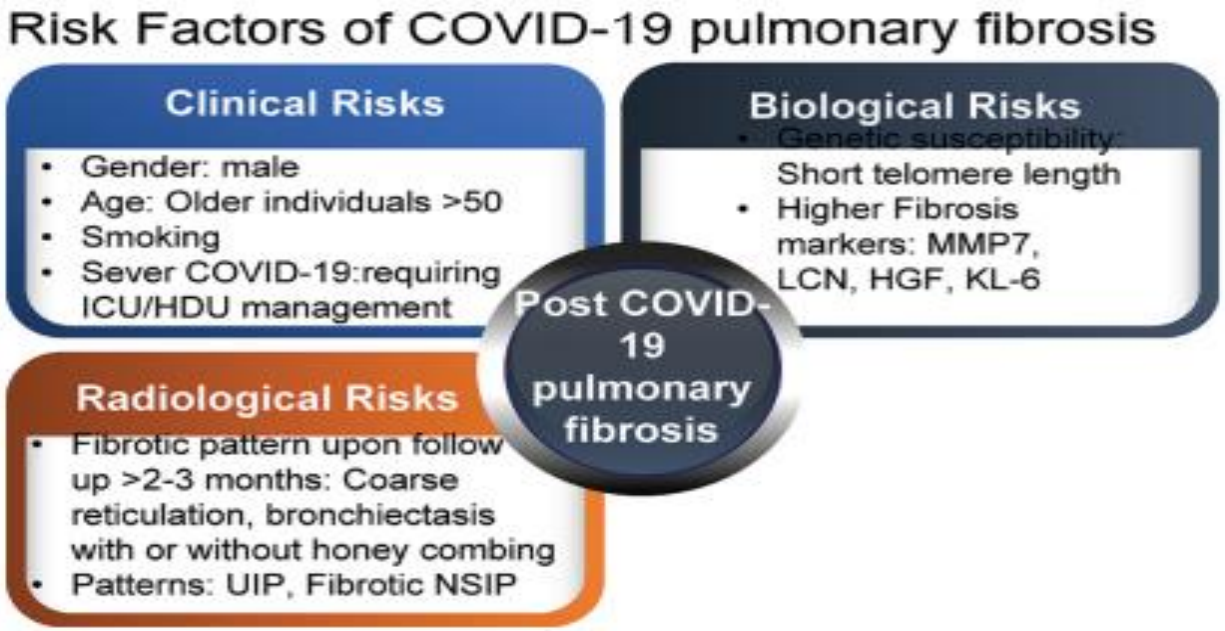


Figure 2: Risk factors for pulmoanry fibrosis. There are clinical, biological, and radiological risk factors. HGF: Hepatocyte growth factor, ICU/HDU: Intensive care unit/high dependency unit, KL-6: Krebs von den Lungen 6, LCN: Lipocalin 2, MMP-7: Matrix metalloproteinase-7, NSIP: Nonspecific interstitial pneumonia, UIP: Usual interstitial pneumonia

N.N.Alrajhi. Post-COVID-19 pulmonary fibrosis: An ongoing concern; Annals of Thoracic Medicine 2023

Patogeneza post COVID-19 plućne fibroze

- Dualna patogeneza:
  - Virusom indukovana subkliničk forma plućne fibroze uz
  - Genetsku predispoziciju

- Direktni uticaj SARS CoV2 na profibroznu kaskadu

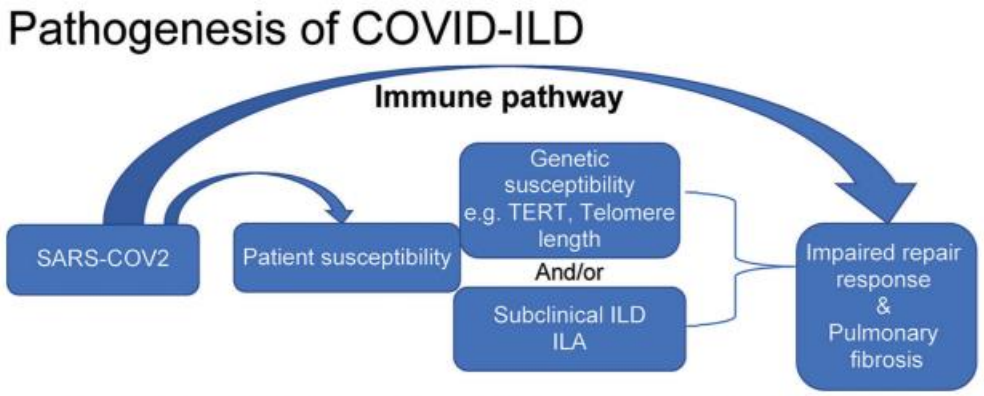


Figure 1: SARS-CoV-2 can cause ILD through either its immunological effect on alveolar epithelial cells or through two-hits hypothesis. in the immunological pathway, SARS-CoV-2 directly binds to ACE2 receptor with subsequent stimulation of the profibrotic cascade, leading to impaired repair response and pulmonary fibrosis. SARS-CoV-2 can also induce lung fibrosis in patients with either genetic predisposition or patients with subclinical ILA. ACE2: angiotensin-converting enzyme 2. ILA: Interstitial lung abnormalities, ILD: Interstitial lung disease, SARS- CoV-2: Severe acute respiratory syndrome coronavirus 2

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Šta znamo o post COVID-19 PF…..

- Prediktori of post-COVID-19 ILD:
  - Starija životna dob,
  - Teži oblik COVID-19,
  - Upotreba ili prolongirano trajanje MV,
  - Pušenje
  - Alkoholizam

- Blagi do umjereni oblik bolesti –potpuna rezolucija

- Teški oblik COVID-19 bolesti može imati dugotrajnu post-COVID-19 ILD

- Dugotrajna upotreba kiseoničke terapije može povećati rizik od nastanka PF

Kako tretirati POST COVID plućnu bolest???

Sistemsko praćenje

- Klinički pregledi
- PFT
- 6MWT
- Indicirane radiološke pretrage (Rtg p/c; HRCT; CTA)
- Referalni centri za ILD

Intervencije

- Intervencije ograničeno korisne do sada:
  - Fizikalna terapija
  - Grupe za potporu
- Kliničke studije:
  - observacione i
  - intervencijske

Tretman

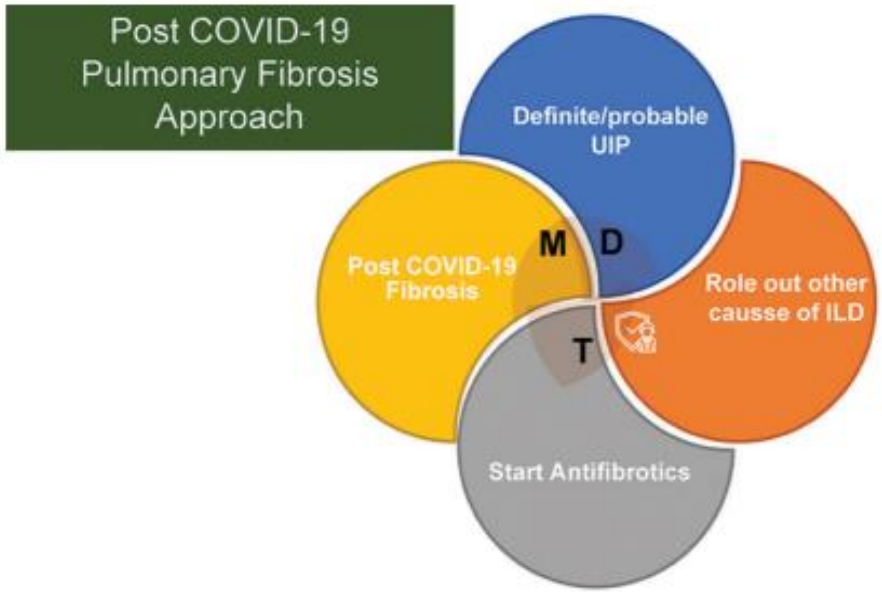

Figure 3: Approach to post-COVID pulmonary fibrosis: To determine the pattern of pulmonary fibrosis. If definite or probable usual interstitial pneumonia, to role out other causes of interstitial lung disease. If all other causes are ruled out, and after multidisciplinary team discussion discussion, consider starting antifibrotics. UIP: Usual interstitial pneumonia, ILD: Interstitial lung disease, MDT: Multidisciplinary team discussion

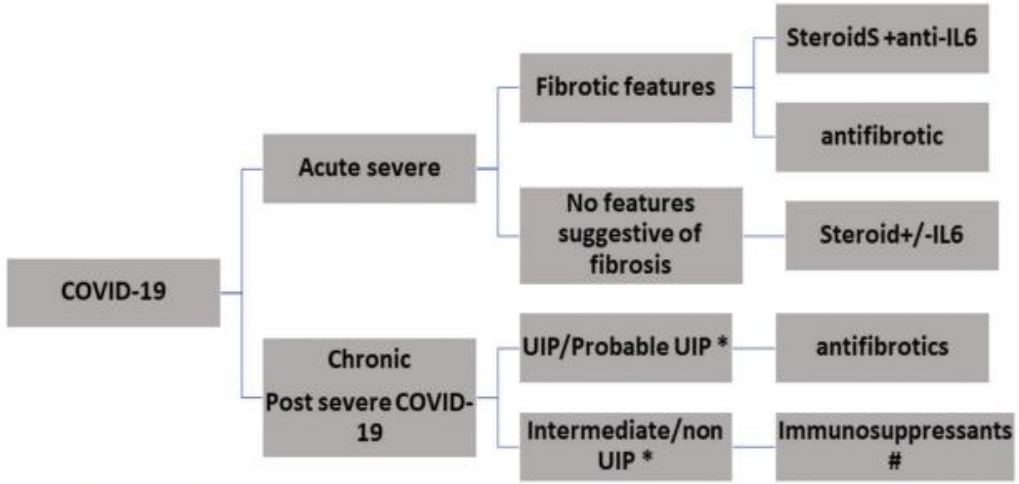

Figure 4: Schematic approach to manage post COVID-ILDs: The approach depends on the acuteness of presentation. Acute COVID-19 is managed by steroid therapy with or without Interleukin-6 therapy. The decision of starting antifibrotic therapy in acute severe COVID-19 depends largely on the radiological appearance of fibrosis described as significant reticulation, severe traction bronchiectasis, and architectural distortion with or with honeycombing. Managing chronic post-COVID-19 interstitial lung disease (ILD) largely depends on the radiological pattern. *After excluding other causes of ILDs. #Antifibrotics can be added if patients experienced progressive phenotype despite immunosuppressant therapy. UIP: Usual interstitial pneumonia, IL-6: Interleukin-6

N.N.Alrajhi. Post-COVID-19 pulmonary fibrosis: An ongoing concern; Annals of Thoracic Medicine 2023

Antifibrozni lijekovi u tretmanu post COVID-19 PF

- Radiološki znaci fibroze i potencijal za progresiju (bez jasnih dokaza PRO/CONTRA)

- PRO: "Honeycombing", iskrivljena plućna arhitektonika, i trakcione bronhiektazije
- CONTRA: "ground-glass opacities" (GGO), organizirajuća pneumonija i pleuralna reakcija

- Tačno vrijeme početka terapije- nepoznato!!!!

- Trakcione bronhiektazije, honecombing, iskrivljena plućna arhitektonika na HRCT i simptomatični pacijenti, koji zahtijevaju kiseoničku terapiju nakon četiri sedmice steroidne terapije mogu biti kandidati za antifibroznu terapiju
- Progresivno opadanje plućne funkcije ili pogoršanje radiološkog nalaza fibroze tokom ambulantnog praćenja –mogu biti kandidati za antifibrozne lijekove

- Nintedanib vs. pirfenidone (nijedan zvanično odobren u ovoj indikaciji)

- Dužina trajanja terapije: najmanje 2 mjeseca sa mogućim produženjem do 6 mjeseci (case-to-case basis)

Salvi SS, et al. 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. Lung India. 2022 Mar-Apr;39(2):177-186.

Kliničke studije u POST COVID-19 ILD

- **OBSERVATIONAL**
- **NCT04416100** Development of Interstitial Lung Disease (ILD) in Patients With Severe SARS-CoV-2 Infection. To investigate COVID-19 survivors through clinical examinations, functional lung examinations, HR-CT scans, and by determining the "immunofibrotic" pattern in peripheral mononuclear cells (PBMCs) 1, 3, and 6 months after discharge
- **NCT05074875** COVID-19 Respiratory Outcomes Registry: To determine if inflammatory process of hypoxemic respiratory failure associated with COVID-19 leads to progressive pulmonary fibrosis: Data collection

Kliničke studije u POST COVID-19 ILD

- **Interventional**
- **NCT04818489** Impact of **Colchicine** on the Clinical Outcome of **COVID**-19 and the Development of **Post-COVID**-19 Pulmonary Fibrosis: Randomized Controlled Clinical Trial
- **NCT04619680** determine the effect of **Nintedanib** on slowing the rate of **lung disease** in patients who have been diagnosed with **COVID**-19, and have ongoing **lung** injury more than 4 weeks from infection (ENDCOVI)
- **NCT04541680 Nintedanib** for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis (NINTECOR)
- **NCT04988282 Systemic corticosteroids** in Post-**COVID**-19 Interstitial **Lung Disease** (ILD) patients who have persistent respiratory symptoms with functional impairment and radiological sequela.
- **NCT04856111 Pirfenidone** vs. **Nintedanib** for Fibrotic Lung Disease After Coronavirus Disease-19 Pneumonia (PINCER)

POST COVID-19 PLUĆNE KOMPLIKACIJE

ZAKLJUČCI

- Plućne vaskularne i parenhimske bolesti su važne komplikacije COVID-19 infekcije
- Oni su povezani sa teškom formom bolesti, ali se javljaju i kod umjerenog i blagog oblika bolesti
- Saznanja o manifestacijama i osnovnim mehanizmima/uzrocima se brzo razvijaju
- Adekvatna evaluacija i monitoring pacijenata je važan za bolje razumijevanje toka bolesti
- Observacione i intervencijske studije koje su u toku će dati odgovore na pitanja i odrediti naš menadžment i poboljšati ishod bolesti

Hvala za pažnju!