PULMONARY SEQUELAE POST COVID 19

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DIVISION

BACKGROUND

SYMPTOMS

PATHOPHYSIOLOGY

RADIOLOGY

LUNG FUNCTION TEST ABNORMALITIES

BIOMARKERS

COVID 19 AND CRD

FOLLOW UP

ONGOING TRIALS

Coronavirus disease 2019 (COVID-19) announced in March 2020 as a pandemic by the World Health Organization (WHO)

The causative agent of COVID-19 is the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Months later, longer-lasting COVID-19 cases started gaining attraction among social support groups ,like Long Haul Covid Fighters,Body Politic Covid-19 Support Group

At first, doctors dismissed their concerns as symptoms related to mental health, such as anxiety, in a phenomenon called “medical gaslighting”

Rita Rubin et al, JAMA October 13,2020,vol 324,number 14

Early data suggested a shorter recovery (eg, two weeks) for those with mild disease, and a longer recovery (eg, two to three months or longer) for those with more severe disease.

https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---24-february-2020

But scenario changed soon

The term long-haul COVID-19 (or post-acute COVID-19 or chronic COVID syndrome or long-COVID) started gaining recognition in the scientific and medical communities

Trisha Greenhalgh : BMJ 2020;370:m3026

The recovery process from COVID-19 exists on a continuum

- **Acute COVID-19**: symptoms of COVID-19 for up to 4 weeks following the onset of illness
- **Ongoing symptomatic COVID-19**: symptoms of COVID-19 from 4 to 12 weeks following the onset of illness
- **Post-COVID-19**: symptoms that develop during or after COVID-19, continue for ≥ 12 weeks, not explained by an alternative diagnosis

https://www.nice.org.uk/guidance/ng188

PULMONARY SYMPTOMS

As the name SARS-Covid 19 suggests ,main target is respiratory system

Many studies across the world has demonstrated persistent respiratory symptoms after covid 19 infection

AUTHOR	STUDY	COUNTRY	RESPIRATORY SYMPTOM
Xiong Q et al	Follow-up survey of COVID-19 patients hospitalized and discharged Telephone based 538 survivor 97(95-102 days)	China	Respiratory symptoms (n = 210, 39%)
Carfì A et al	Follow up study 179 patients Mean duration 60.3 days	Italy	32% had 1 or 2 symptoms 55% had 3 or more dyspnea (43.4%) chest pain (21.7%)
Halpin S J et al	Cross sectional study 100 survivors Discharged from a large University hospital Mean 48 days post discharge	UK	Breathlessness (65.6% in ICU group and 42.6% in ward group)
Yan et al	Follow up study 2 weeks post discharge 337 survivors	China	Cough(9.2%) , Dyspnoea(2.1%)

Authors	Study design	Cuntry	Symptoms
Huang C, Huang L et al	Ambi-directional cohort study 1733 of 2469 discharged patients with COVID-19 Median duration 186 days(175-199 days)	Wuhan, China	5% chest pain,26% dyspnea
Nehme M et al	Follow up study 669 enrolled Duration:45 days	Geneva, Switzerland	Cough :common early in the clinical course. At 30 to 45 days (mean, 43 days) 32% reported one or more persistent symptom Commonest persistent symptom dyspnea

Author	Study design	Country	Symptoms
Arnold et al. (2020).	Observational study (n = 110) Median of 83 days after hospital discharge	Bristol, England	Dyspnea (39%) Cough
Miyazato et al. (2020)	Follow up study (n = 63)	Tokyo, Japan	After 60 days: Dyspnea (17.5%), Cough (7.9%)
			After 120 days: Cough (6.3%)

PATIENT CHARACTERISTICS

A study of 180 survivors found that 53.1% developed symptoms of long-haul COVID-19 for at least 125 days since symptom onset, which was not associated with gender, smoking, comorbidities, or medication use

Maria Skaalum Petersen et al. Clinical Infectious Diseases. 2020

PATHOPHYSIOLOGY

Enveloped virus

Infects host through a series of viral spike proteins

Host proteaseTMPRSS2, reveals the fusion domain of the spike protein

It allows attachment to the angiotensin-converting enzyme-2 (ACE2) receptor on the host cell

Endocytosis occurs

Viral genome is released into the host cell

Virus hijacks the host cellular machinery to replicate and release viral particles extracellularly

Viral genome is released into the host cell

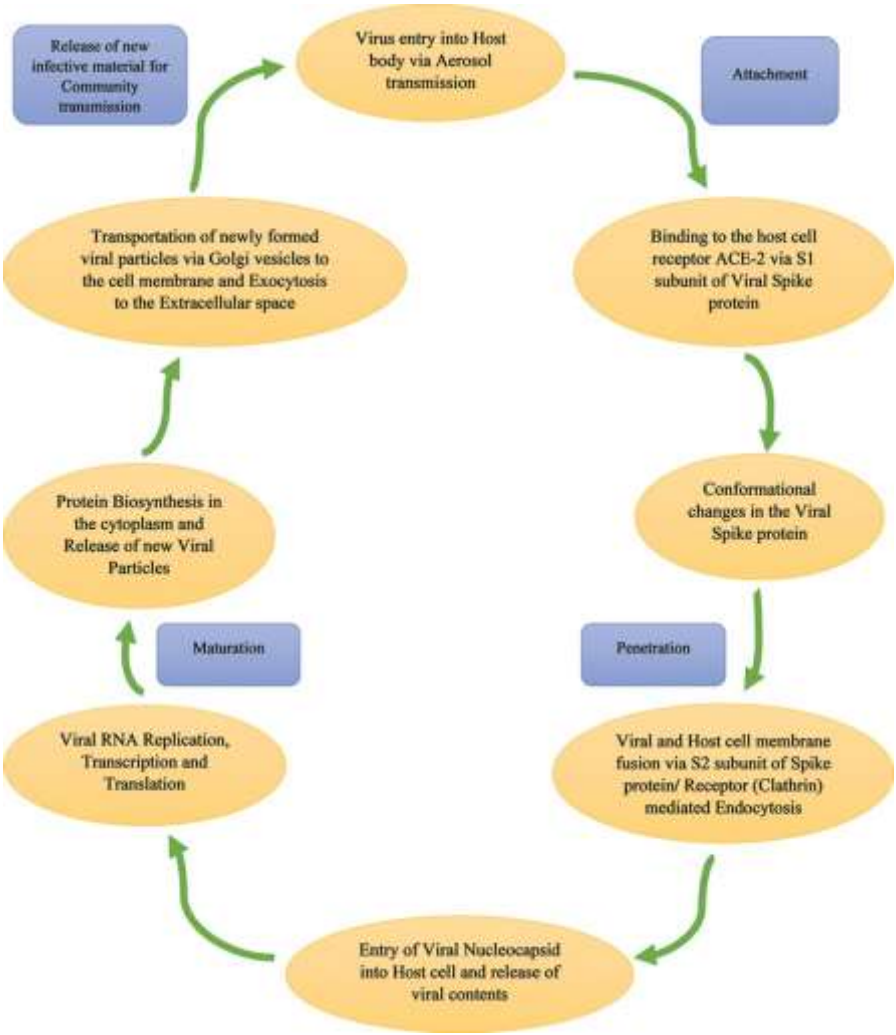
Virus hijacks the host cellular machinery to replicate and release viral particles extracellularly

Results in infection of neighboring cells

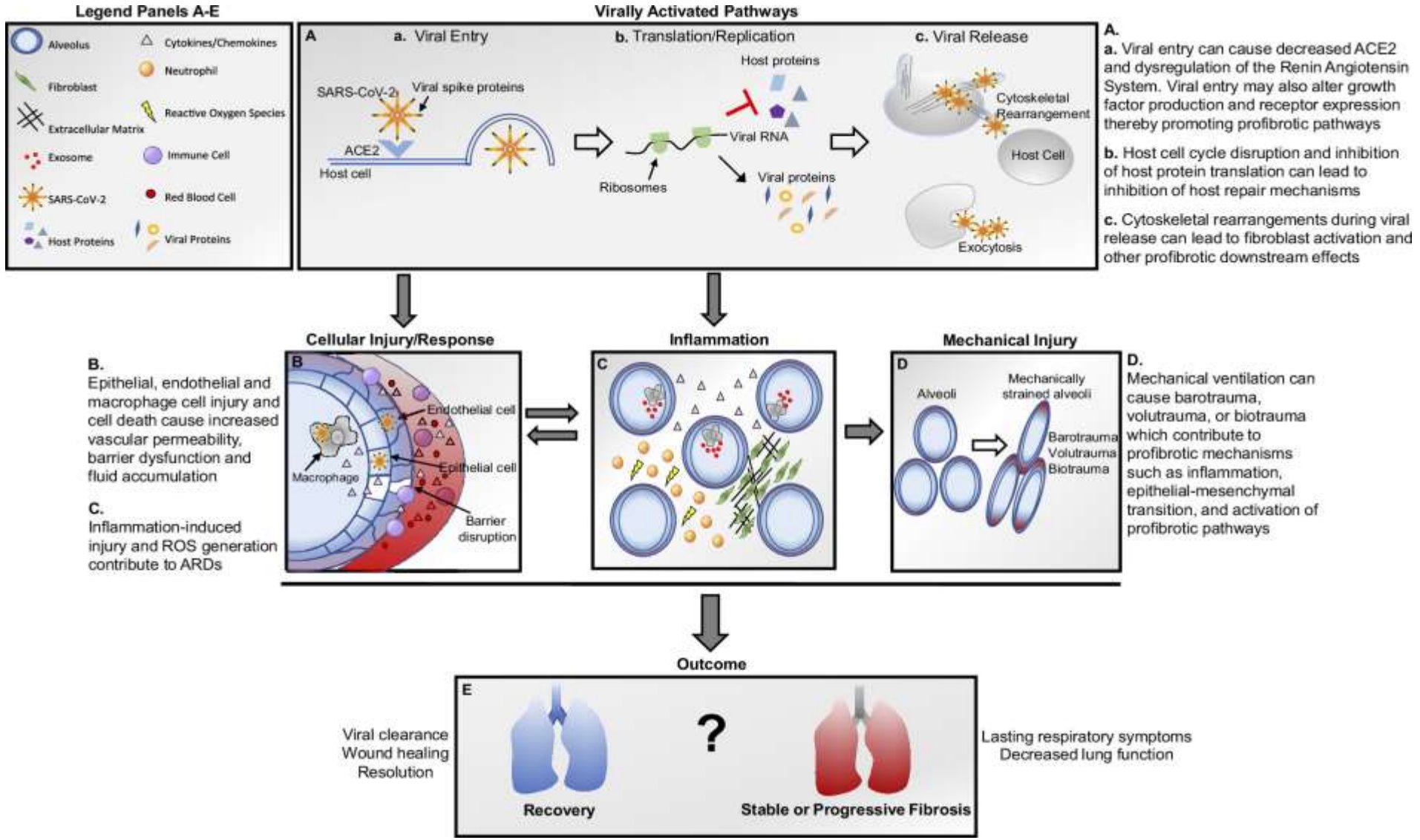
Virus is believed to infect several target cells, including type II pneumocytes, and alveolar macrophages in the lungs

Lindsay T mcDonald Am J Physiol Lung Cell Mol Physiol 320: L257–L265, 2021

The severe acute respiratory syndrome coronavirus-2 life cycle.



Anant Parasher Postgrad Med J doi:10.1136/postgradmedj-2020-138577



LindsayT.McDonald ajplung.00238.2020

Modern Pathology (2020) 33:2128–2138
https://doi.org/10.1038/s41379-020-0603-3

REVIEW ARTICLE

A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression

Samuel B. Polak[1] · Inge C. Van Gool[1] · Danielle Cohen[2] · Jan H. von der Thüsen[3] · Judith van Paassen[1]

Received: 13 May 2020 / Revised: 6 June 2020 / Accepted: 6 June 2020 / Published online: 22 June 2020

- 42 articles in qualitative analysis
- Gross examination for 92 patients
- Pulmonary histopathology for 129 cases

GROSS EXAMINATION

Finding of gross examination	Cases
Increased lung weight	82(88%)
Diffusely congested and edematous parenchyma	76(83%)
Haemorrhagic changes	20(22%)
Macroscopic emboli	9(10%)

PULMONARY HISTOPATHOLOGY

Scored for the presence or absence of epithelial, vascular, and/or fibrotic patterns of lung

- Epithelial pattern
  - In 110(88%).
  - Interstitial inflammatory infiltrate:predominantly of lymphocytes and/or plasma cells
  - Intra-alveolar infiltrate:Macrophage

- Vasculopathy:

  Present in 76(59%)

  Microthrombi and proteinaceous and fibrinous exudates.

  Microthrombi were not consistently linked to intra-alveolar fibrin

  Fibrotic pattern:

  Obsereved in 28 patients (22%).

  typified by interstitial fibrosis.

  The presence of fibrosis (occurring separately or in combination with epithelial and/or vascular injury) was not associated with mechanical ventilation

47 cases (60%) had two or more histological pattern, with the highest degree of overlap between the epithelial and vascular patterns (in 32cases)

- Correlation with time:

  Epithelial pattern of lung injury :Occurs early, may persist throughout the clinical coarse

  Gradually declining by 28 days after the onset of symptoms

  Vascular pattern :can occur early after the onset of symptoms

  Fibrotic pattern: observed primarily three weeks from the onset of symptoms

Three histological patterns can be present at different times but can also be present simultaneously

NEUROLOGICAL CONTRIBUTION

Damage of the brainstem’s respiratory center, which expresses high levels of angiotensin-converting enzyme 2 (ACE2; receptor of SARS-CoV2), has been proposed to worsen respiratory symptoms of COVID-19

Sonu Gandhi et aChem. Neurosci. 11, 10, 1379-1381

AUTOIMMUNE FEATURES

It has been suggested that T-cells dysfunction may promote long-haul COVID-19 pathophysiology in a similar manner in autoimmune diseases.

- Higher incidence of females.
- Hypothetical mechanism may be molecular mimicry,as H CoV specific T cells can cross react to myelin in patients with multiple sclerosis.

Annika C Karlsson et al. Sci. Immunol. 5, eabe8063(2020)

B-cells may also be involved in long-haul COVID-19 autoimmunity, as evidenced by the presence of self-reactive autoantibodies in patients with COVID-19.

Zhao-Wei Gao, Hui Zhong Zhang et al.
Autoimmunity Reviews 20(2021)102754

Radiological study of COVID-19 long-haulers has revealed an increase in [18F]FDG uptake which signifies persistent inflammation

In the bone marrow and blood vessels in 80% and 60% of participants

These reports imply that unresolved inflammation may partly account for long-haul COVID-19 pathophysiology

M Sollini et al. Eur J Nucl Med Mol Imaging

RADIOLOGY

Chest radiology in different studies have shown persistent abnormalities following covid 19.

Dehan Liu , Wanshu Zhang in a short term observational study observed course of change in radiology.

STUDY POPULATION:

Patients with COVID-19 pneumonia confirmed by RT-PCR

discharged from the hospital between 5 February 2020 and 10 March 2020

Critical patients were excluded from the study.

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RADIOLOGY FOLLOW UP:

chest CT scans done during the 1st, 2nd, and 3rd weeks after discharge

The radiological characteristics of all patients were collected and analysed

The cumulative percentage of complete radiological resolution at different time points

	n = 149.
Chest CT at discharge	12 (8.1%)
The 1st CT follow-up	62 (41.6%)
The 2nd CT follow-up	75 (50.3%)
The 3rd CT follow-up	79 (53.0%)

Liu et al.Respiratory Research (2020) 21:125

Dynamic CT changes

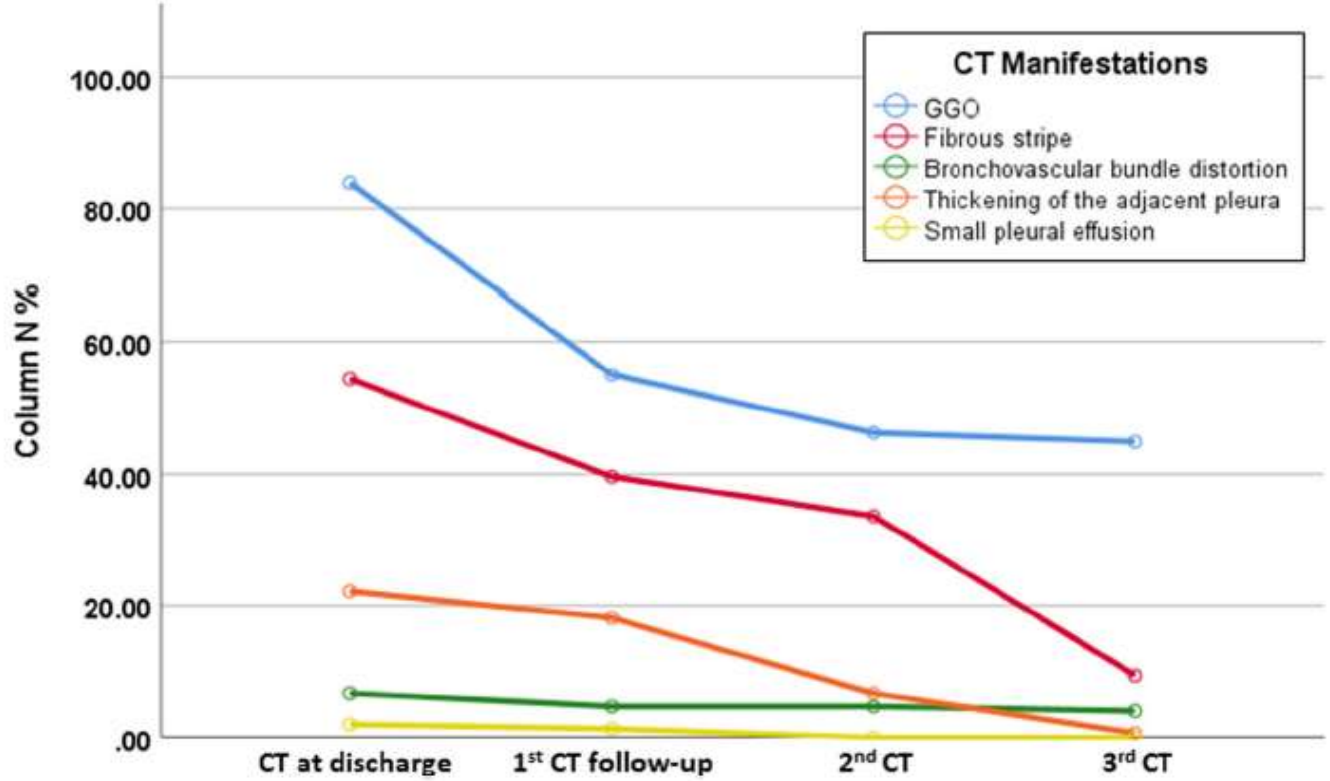


Fig. 1 Dynamic changes of chest CT manifestation in different timepoint after discharged. Note: The predominant pattern were ground-glass opacity (GGO), fibrous stripe. With time, the positive count of GGO, fibrous stripe and thickening of the adjacent pleura gradually decreased, while GGO and fibrous stripe showed obvious resolution during the first week and the third week after discharge, respectively

Liu et al.Respiratory Research (2020) 21:125

Complete resolution in respect to age, gender, CT score at discharge

	Complete radiological resolution (n)		*p*-value[a]
	Yes	No	
Age (y)			
≤ 44	58	26	**< 0.001**
> 44	21	44	
Gender			
Male	39	28	0.251
Female	40	42	
CT score at discharge			
≤ 1	60	54	0.864
> 1	19	16	

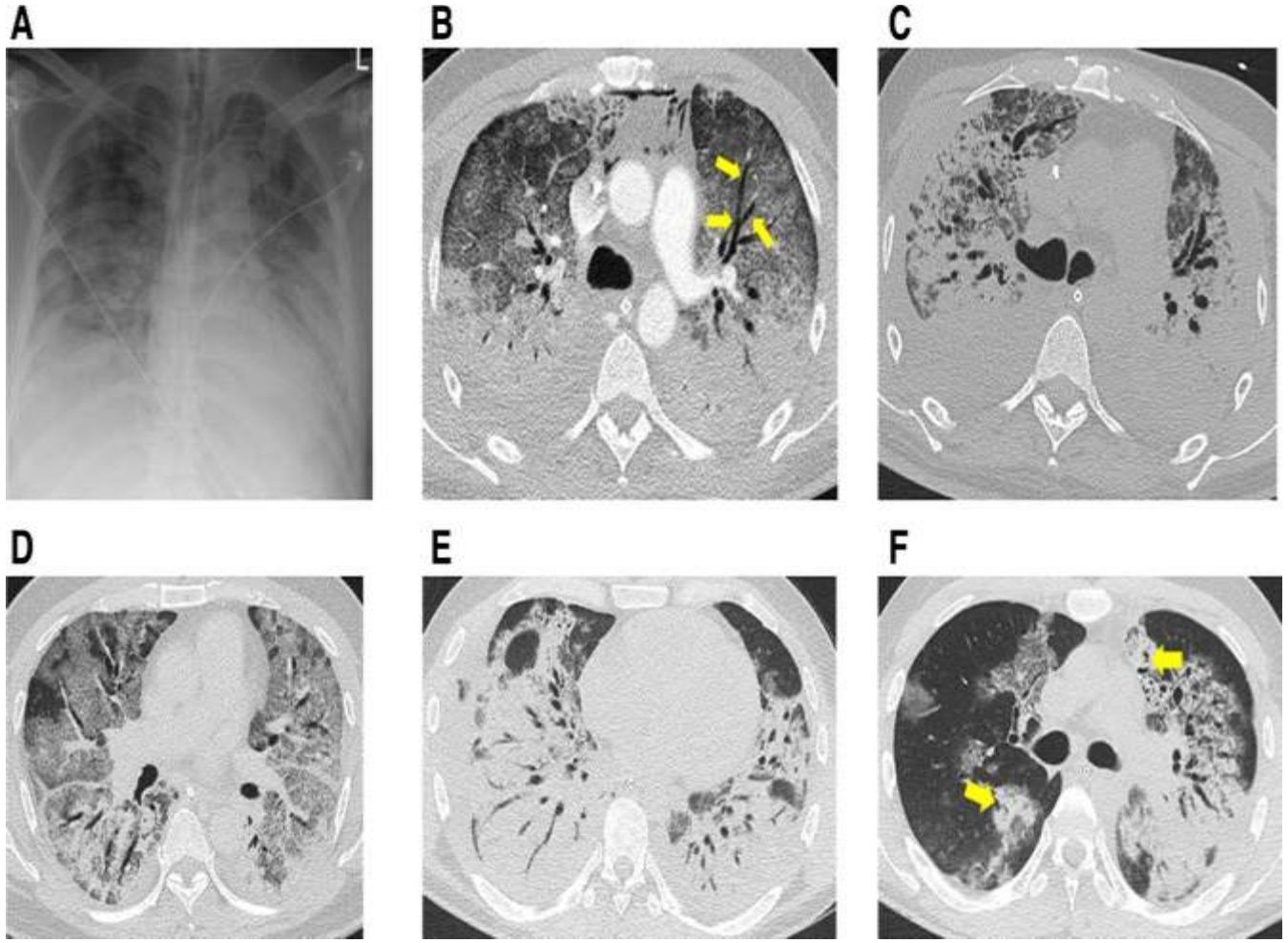
[a]Chi-square test

Liu et al.Respiratory Research (2020) 21:125

Morphological pattern of lung disease on CT scan are regions of ground-glass opacification and consolidation, which variably comprise foci of oedema, organising pneumonia and diffuse alveolar damage

The radiological changes in COVID-19 pneumonia do not appear to resolve fully in all patients and in some, inflammation matures to form fibrosis.

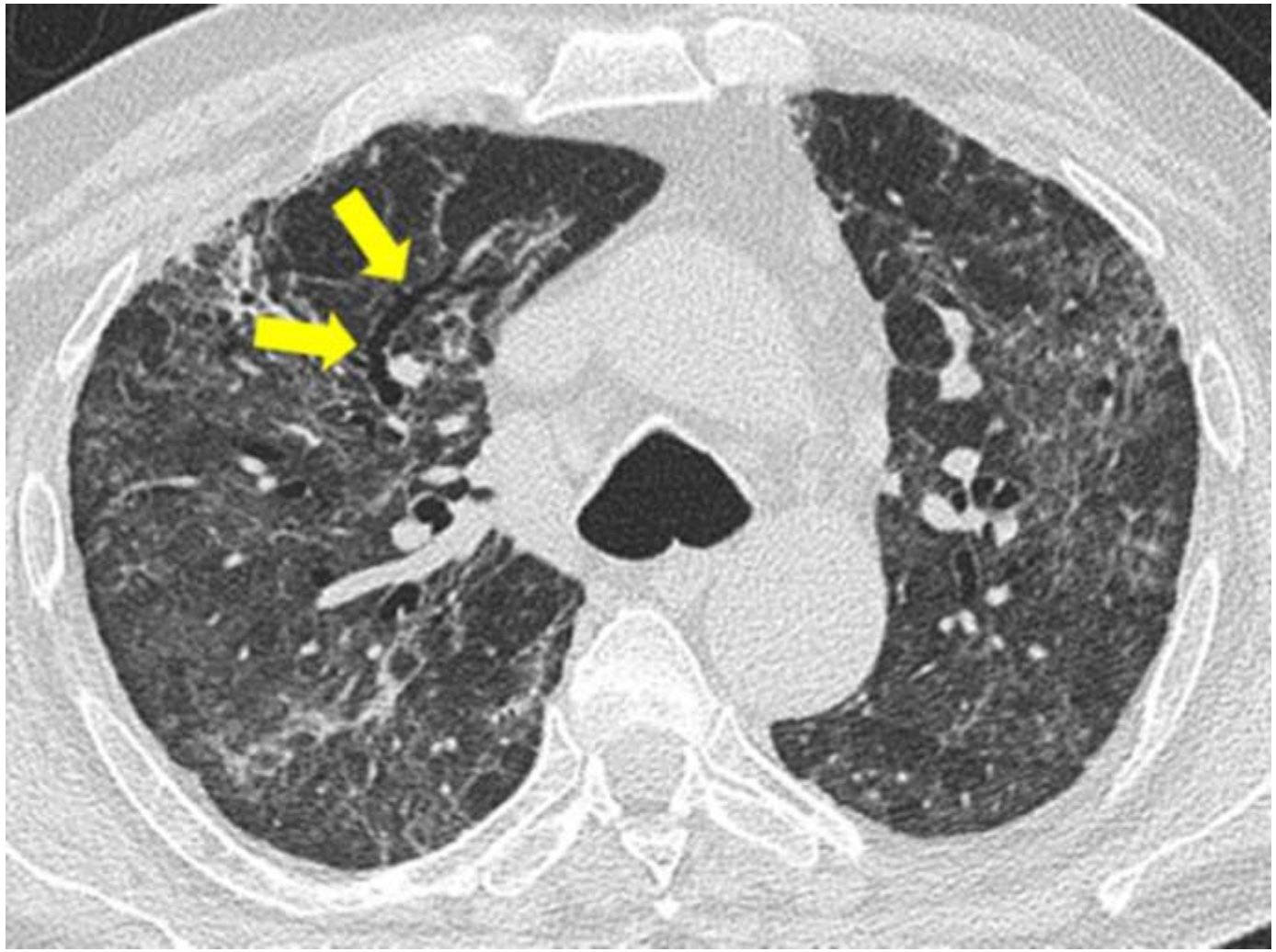
George PM et al. Thorax2020;75:1009–1016.



. **(A) Plain chest radiograph in a male patient with COVID-19 pneumonia referred for extracorporeal membrane oxygenation support.**
(B) CT images showing broadly symmetrical air space opacification with dependent dense parenchymal opacification and extensive ground-glass opacification with thickened interlobular and intralobular septa (the 'crazy-paving' pattern) in the non-dependent lung. (C) CT performed 10 days later again showing widespread air space opacification but now with 'varicose' dilatation (non-tapering) of airways in the left upper lobe indicative of developing pulmonary fibrosis. (D) Classical 'crazy-paving' appearance in COVID-19. There is patchy but very extensive ground-glass opacification with superimposed fine thickening of interlobular and intralobular septa throughout both lungs. (E) A patient with COVID-19-related acute respiratory distress syndrome (ARDS) with image section though the lower zones showing characteristic findings of ARDS with symmetrical air space opacification but with a gradient of increasing density from the ventral to the dorsal lung. (F) Image just below the carina demonstrating foci of non-dependent consolidation (*arrows*), conceivably denoting areas of organising pneumonia.

THORAX

CT in COVID-19 extubated survivor: a study performed during recovery (26 days after onset of COVID-19 pneumonia).



During recovery (26 days after onset of COVID-19 pneumonia). Image section at the level of the carina demonstrating widespread ground-glass opacification and considerable architectural distortion. There is definite CT evidence of fibrosis—varicose dilatation ('traction bronchiectasis') of the anterior segmental bronchus in the right upper lobe (arrows).

Peter M George et al. Thorax 2020;75:1009-1016

THORAX

Xun Dinga et al conducted a study

- To evaluate lung abnormalities
- In thin-section computed tomographic (CT) scans
- To correlate findings to duration of symptoms

Severity of pneumonia was not correlated with radiological finding.

Scans were categorized according to time the period between the onset of initial symptoms and the CT scans:

stage-1 (0–4 days n=47)

stage-2 (5–9 days n=54)

stage-3 (10–14 days n=67)

stage-4 (15–21 days, n=68)

stage-5 (22–28 days, n=59)

and stage-6 (＞28 days, n=53)

Distribution and frequency of the pulmonary lesions on CT at different stages.

	Stage-1 (n = 47)	Stage-2 (n = 54)	Stage-3 (n = 67)	Stage-4 (n = 68)	Stage-5 (n = 59)	Stage-6 (n = 53)
Distribution of pulmonary lesions						
No lesion	10 (21.2 %)	1 (1.8 %)	2 (2.9 %)	2 (2.9 %)	1 (1.7 %)	1 (1.8 %)
Peripheral	30 (63.8)	36 (66.6 %)	41 (61.2 %)	37 (54.4 %)	31 (52.4 %)	30 (56.6 %)
Central	1 (2.1 %)	1 (1.8 %)	1 (1.5 %)	0 (0%)	1 (1.7 %)	0 (0 %)
Diffuse	6 (12.7 %)	16 (29.6 %)	23 (34.3 %)	29 (42.6 %)	26 (44.1 %)	22 (41.5 %)
Involvement of the lung						
No involvement	10 (21.2 %)	1 (1.8 %)	2 (2.9 %)	2 (2.9 %)	1 (1.7 %)	1 (1.8 %)
Single lobe	16 (34.0 %)	11 (20.3 %)	8 (11.9 %)	1 (1.5 %)	4 (6.8 %)	2 (3.8 %)
Unilateral multilobe	1 (2.1 %)	1 (1.8 %)	2 (2.9 %)	0 (0 %)	1 (1.7 %)	0 (0 %)
Bilateral multilobe	20 (42.5 %)	41 (75.7 %)	55 (82.1 %)	65 (95.6 %)	53 (89.8 %)	50 (94.3 %)
GGO	36 (76.5 %)	48 (88.8 %)	61 (91.0 %)	59 (86.7 %)	57 (96.6 %)	52 (98.1 %)
Crazy-paving pattern	17 (36.1 %)	31 (57.4 %)	42 (62.7 %)	38 (55.9 %)	33 (55.9 %)	28 (52.8 %)
Consolidation	12 (25.5 %)	37 (68.5 %)	42 (62.7 %)	51 (75.0 %)	30 (50.8 %)	16 (30.2 %)
Linear opacities	3 (6.3 %)	14 (25.9 %)	32 (47.7 %)	51 (75.0 %)	49 (83.1 %)	39 (73.6 %)
Air bronchogram	8 (17.0 %)	27 (50.0 %)	27 (40.3 %)	34 (50.0 %)	18 (30.5 %)	13 (24.5 %)
Cavitation	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Bronchiectasia	3 (6.3 %)	7 (12.9 %)	13 (19.4 %)	23 (33.8 %)	19 (32.2 %)	24 (45.2 %)
Pleural effusion	2 (4.2 %)	5 (9.2 %)	14 (20.9 %)	19 (27.9 %)	11(18.6 %)	8 (15.1 %)
Pericardial effusion	0 (0 %)	0 (0 %)	3 (4.4 %)	1 (1.5 %)	1 (1.7 %)	0 (0 %)
Lymphadenopathy	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Pneumothorax	0 (0 %)	0 (0 %)	1 (1.5 %)	0 (0 %)	1 (1.7 %)	2 (3.8 %)

X Ding et al. European Journal of Radiology 127 (2020) 109009

Author	Study design	country	finding
Qiongjie Hu et al	Retrospective , observational study (n=46)	China	After 10 day (the 2nd week), 12 (60 %) of 20 patients had irregular linear opacities with or without associated ground-glass opacity or consolidation. Mixed and predominantly reticular patterns were noted from the 14th day in 7 of 20 patients (45 %). At 22–31 days after the onset of initial symptoms, the lesions were completely absorbed in only 2 of 7 patients.
Yu-miao Zhaoa et al	Follow up study 3 months , 55 patients	China	70.90% patients had residual abnormality in CT thorax after 3 months. pure GGO (7 of 55, 7.27%), interstitial thickening (15 of 55, 27.27%), and crazy paving (3 of 55, 5.45%) were the most common CT features found

Authors	Study design	Country	Finding
Seyed Mohammad Hossein Tabatabaei et al	retrospective study (n =52) 3 months difference	Iran	The most common radiological pattern on initial CT was GGO (24/52, 46.2%), followed by consolidation (14/52, 26.9%) and mixed pattern (14/52, 26.9%). Most common radiologic pattern in the patients with residual disease(n=22,42.3%) were GGO (12/22, 54.5%), followed by mixed GGO and subpleural parenchymal bands (7/22, 31.8%), and pure subpleural parenchymal bands (3/22, 13.7%)
Huang C, Huang L et al	ambidirectional cohort study 1733 of 2469 discharged patients with COVID-19 Median duration 186 days(175-199 days)	China	At least one CT abnormality in 52% patient not requiring O2 support and in 54% of patients requiring O2 or NIV support. The most common abnormal CT pattern was pulmonary interstitial change (GGOs and irregular lines)

PULMONARY FUNCTION ABNORMALITIES

Persistent impairment of pulmonary function and exercise capacity have been known to last for months or even years in the recovered survivors from other coronavirus pneumonia (severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

In the follow-up studies lasting from half a year to two years in the rehabilitating SARS patients impaired DLCO was the most common abnormality, ranging from 15.5% to 43.6%, followed by defected TLC, ranging from 5.2% to 10.9%.

Hui DS et al. Thorax 2005; 60: 401–409

Batawi S et al.*Health Qual Life Outcomes* 2019; 17:101

Authors	Study	Country	Finding
Yu-miao Zhaoa et al	Follow up study 3 months 55 patients	China	lung function abnormalities were detected in 14 patients (25.45%). Anomalies were noted in TLC of 4 patients (7.27%), FEV1 of 6 patients (10.91%), FVC of 6 patients (10.91%), DLCO of 9 patients (16.36%), and small airway function in 7 patients (12.73%).
Swiss COVID-19 lung study Sabina A. Guler et al	multicentre, prospective observational cohort study 4 mothsd follow up	Switzerland	Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and DLCO were significantly lower in patients after severe/critical COVID-19 6-min walk distance (6MWD) was 120 m lower in the severe/critical disease group

Authors	Study	country	Finding
Xiaoneng Mo et al	Cross sectional study Duration from onset of disease to pulmonary function test was 20±6 days in cases with mild illness, 29±8 days in cases with pneumonia and 34±7 days in cases that presented severe pneumonia.	China	Anomalies were noted in DLCO% in 51 cases (47.2%), total lung capacity (TLC) in 27 (25.0%), forced expiratory volume in the first second (FEV_1) in 15 (13.6%), forced vital capacity (FVC) in 10 (9.1%), FEV_1/FVC in 5 (4.5%), and small airway function in 8 (7.3%).

Mattia Bellan et al	Prospective cohort study Duration: 4 month Inclusion criteria: Patients hospitalized for COVID-19 (n=238)	Northern Italy	D_{LCO} was reduced to less than 80% of the estimated value in 113 patients (51.6%) and less than 60% in 34 patients (15.5%). 128 patients (53.8%) had functional impairment.

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis

R. Torres-Castro[a,b,*], L. Vasconcello-Castillo[a,b], X. Alsina-Restoy[c,d], L. Solis-Navarro[a], F. Burgos[c,d,e], H. Puppo[a,b], J. Vilaró[b,f]

A systematic review of 5 database

[(Embase, PubMed/MEDLINE, Web of Science, CINAHL, Cochrane Register of Clinical Trials(CENTRAL)]

Studies using lung function test to assess post covid 19

Initial search included 1973 studies

Seven articles met inclusion criteria

Total 380 post infection patients were included

Sample size varied between 18 to 110.

PREVALENCE

- Altered diffusion capacity of the lungs for carbon monoxide (DL_{CO}) :0.39 (CI 0.24–0.56, $p < 0.01$, $I^2 = 86\%$)

- Restrictive pattern: 0.15 (CI 0.09–0.22, $p = 0.03$, $I^2 = 59\%$)

- obstructive pattern : 0.07 (CI 0.04–0.11, $p = 0.31$, $I^2 = 16\%$)

BIOMARKERS

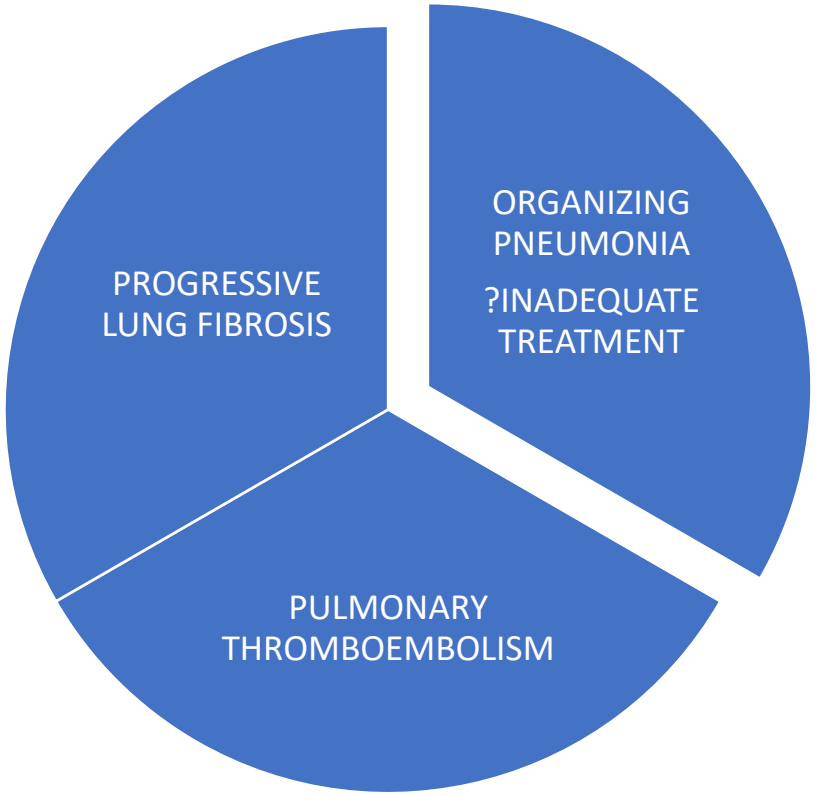
AUTHORS	STUDY	COUNTRY	FINDING
Y. M. Zhao et al. 2020	Follow up study 3 months after hospital discharge (N=55)	Henan Province, China	↑ BUN ↑ D-dimer No changes in CRP, albumin, or glucose
Mandal et al. (2020).	Follow up study Median of 54 days after hospital discharge. (N = 384)	London, U.K	↓ lymphocytes ↑ D-dimer ↑ CRP No changes in WCC, platelets, ferritin, creatine, ALT, AST, or glucose.

Authors	Study	Country	Finding
Townsend et al. (2020).	Observational study (n= 128) 6 weeks after discharge or acute symptom	Dublin, Ireland	No changes in leukocytes, neutrophils, lymphocytes, LDH, CRP, IL-6, or CD25.
Minhua Yu et al	retrospective study Lung fibrosis(n=14) vs non fibrosis group(n=18)	Wuhan, China	C-reactive protein (53.4 mg/L vs. 10.0 mg/L, *p* = 0.002) and interleukin-6 (79.7 pg/L vs. 11.2 pg/L, *p* = 0.04) higher in patients with lung fibrosis

COVID & CRD

Tak Kyu Oh and In-Ae Song	population-based cohort study. otal 122,040 individuals, 36,365 individuals were diagnosed with CRD between 2015 and 2019: COPD (4488, 3.6%), asthma (33,858, 27.2%), ILD (421, 0.3%), lung cancer (769, 0.6%), lung disease due to external agents (437, 0.4%), OSA (550, 0.4%), and TB (608, 0.5%)	South Korea	patients with ILD had 1.63-fold (odds ratio [OR] 1.63, 95% confidence interval [CI] 1.17–2.26; $P = 0.004$) and OSA 1.65-fold higher (OR 1.65, 95% CI 1.23–2.16; $P < 0.001$) incidence of COVID-19. Individuals with COPD 1.56-fold (OR 1.56, 95% CI 1.06–2.2; $P = 0.024$) and lung disease due to external agents had 3.54-fold (OR 3.54, 95% CI 1.70–7.38; $P < 0.001$) higher risk of hospital mortality

TRIDENT OF MALADIES



Massive pulmonary embolism following recovery from COVID-19 infection: inflammation, thrombosis and the role of extended thromboprophylaxis

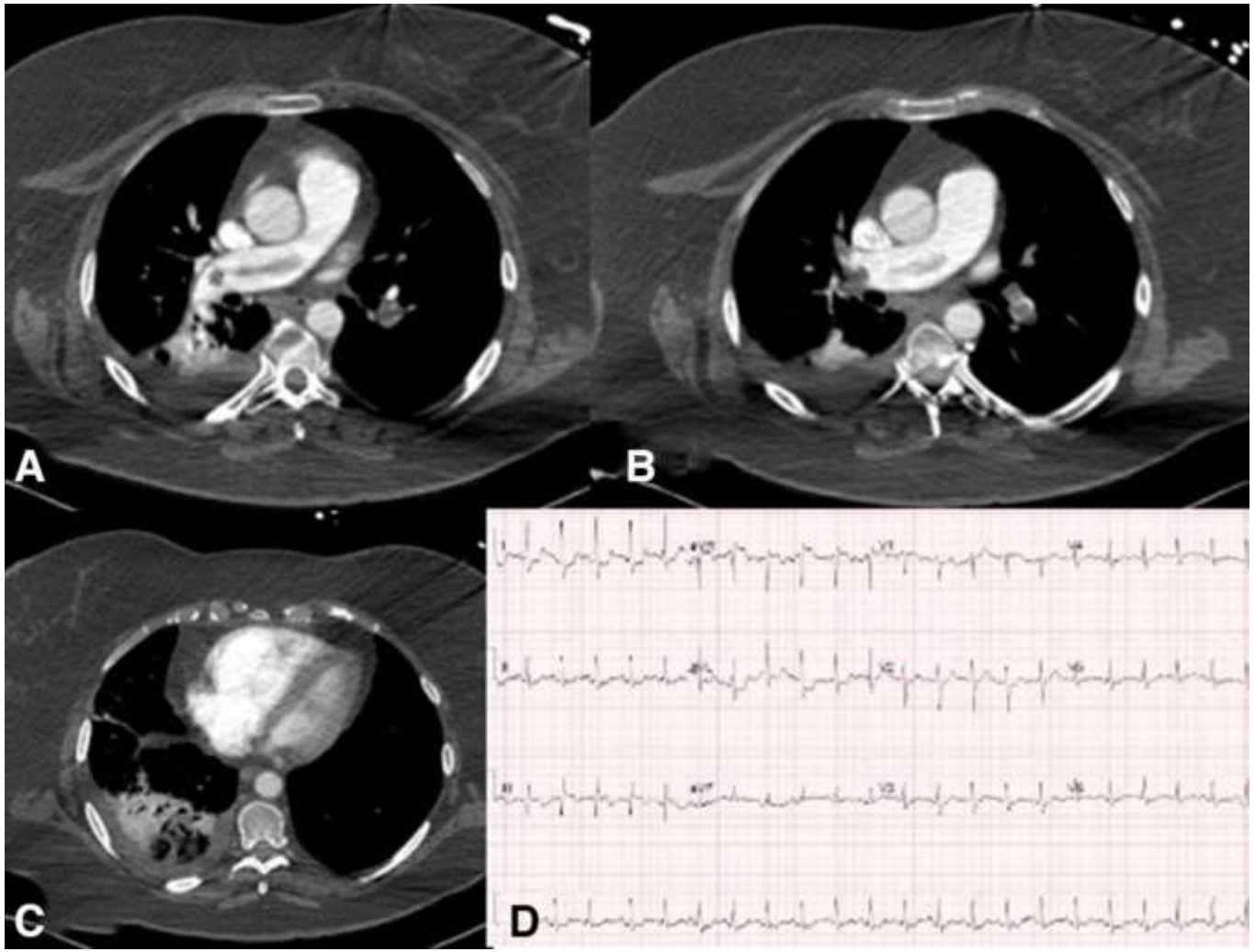
Prakash Vadukul [1], Deepak S Sharma [1] and Paul Vincent [2]

Correspondence to Dr Deepak S Sharma; deepu84in@gmail.com

CASE SCENARIO

- A 52-year-old woman with a background of obesity and undiagnosed type 2 diabetes mellitus.
- Mechanical ventilation , RRT
- Discharged after 3 weeks of hospital stay
- Without any anticoagulation
- Presented after one week with chest pain,breathlessness

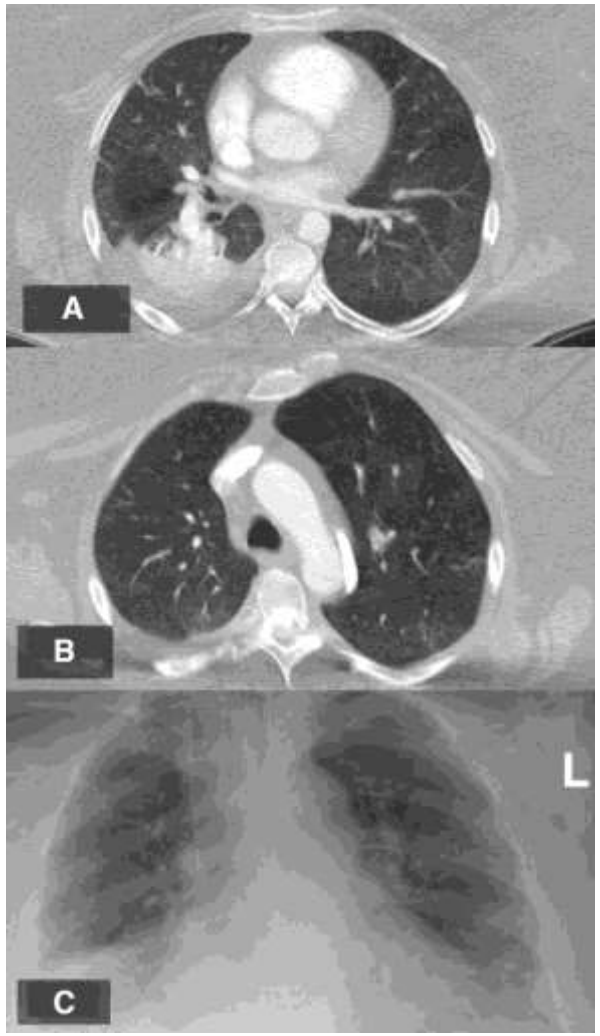
CTPA vascular/soft tissue windows. —(A) saddle embolus component; (B) large volume bilateral pulmonary emboli; (C) right heart enlargement (compared with the left ventricle).



Prakash Vadukul et al. BMJ Case Rep 2020;13:e238168

BMJ Case Reports

(A) CTPA lung window right basal pleural effusion and posterior ‘wedge’ infarction.



Prakash Vadukul et al. BMJ Case Rep 2020;13:e238168

BMJ Case Reports

- Pulmonary emboli has been reported frequently in COVID-19 and are often noted in patients with COVID-19 without other standard risk factors, suggesting that it is an independent risk factor for VTE

- The paucity of deep venous thrombosis (DVT) or other sources of VTE in COVID-19 patients with PE may suggest that, at least in some cases, pulmonary thrombosis rather than embolism is the underlying lesion in these patients.

- Interestingly, the coagulation activation pattern in COVID-19 ARDS patients in the ICU was not the same as in non-COVID-19 ARDS patients . Whereas D-dimers levels were less elevated, PT, activated partial thromboplastin time (aPTT), and AT were within normal ranges, and fibrinogen was higher

Helms J et al. Intensive Care.Med.2020

- Nonetheless, autopsy of 12 consecutive patients admitted to an academic medical center in Germany revealed DVT in 7 of 12 patients (58%) in whom VTE was not suspected before death.
- The prevalence of DVT in COVID-19 patients may, therefore, have been underestimated because of the lack of repeated screening in these patients. The authors also reported that PE was the direct cause of death in one-third of patients, confirming the clinical relevance of this complication

Wichmann D et al. Ann Intern Med. 2020.

Another autopsy study in 11 COVID-19 patients found that death may be caused by the thrombosis observed in segmental and subsegmental pulmonary arterial vessels in all patients, despite the use of prophylactic anticoagulation

high degree of clinical suspicion in diagnosing DVT should be adopted in these patients based on both clinical manifestations and laboratory data.

Lax SF et al. Ann Intern Med. 2020

Review Article

Post-COVID lung fibrosis: The tsunami that will follow the earthquake

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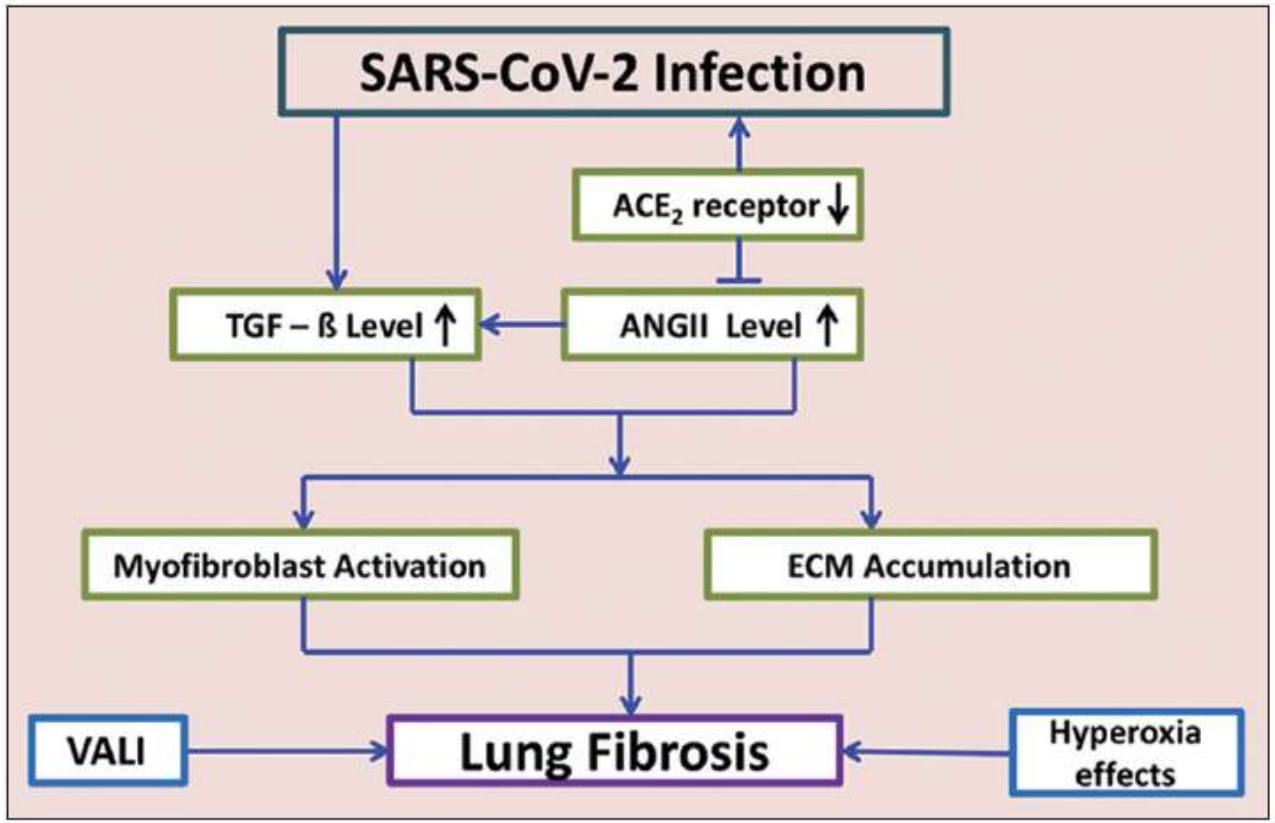
- SARS-CoV-2-associated ARDS is phenotypically distinct from conventional ARDS, characterised by profound hypoxaemia, relatively preserved lung compliance and significant ventilation/perfusion mismatch.

- The majority of patients with ARDS have CT evidence of residual pulmonary fibrosis as well as functional impairment.

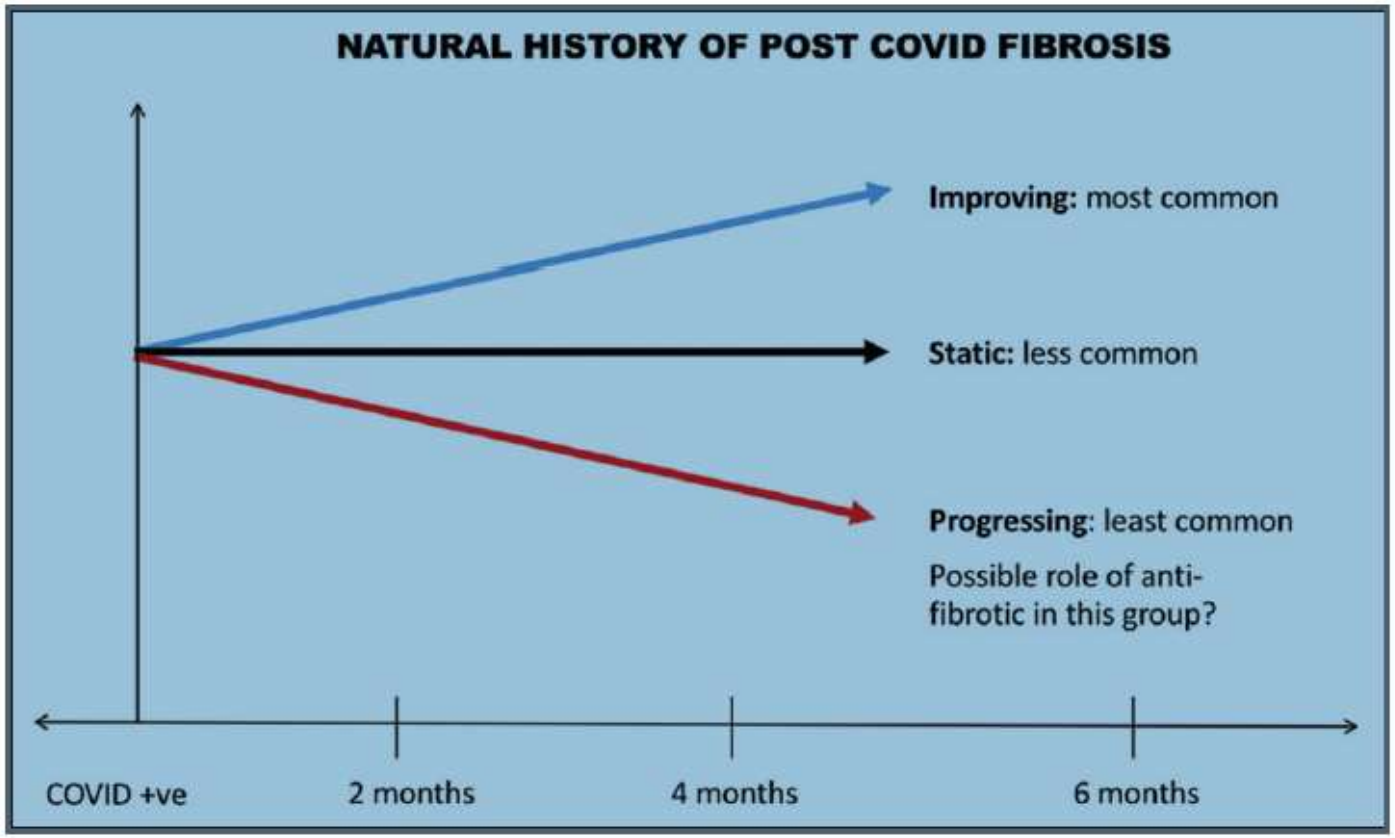
- It is possible that some COVID-19 ICU survivors will experience persistent physiological impairment and radiological abnormalities

George PM, et al. Thorax 2020;**75**:1009–1016



Lung fibrosis mechanism

Z F Udwadia et al.Lung India . Volume 38 . March 2021



Z F Udwadia et al. Lung India . Volume 38 . March 2021

Role of antifibrotic

COVID and IPF share many common demographic factors, disproportionately affecting males, the elderly, and smokers

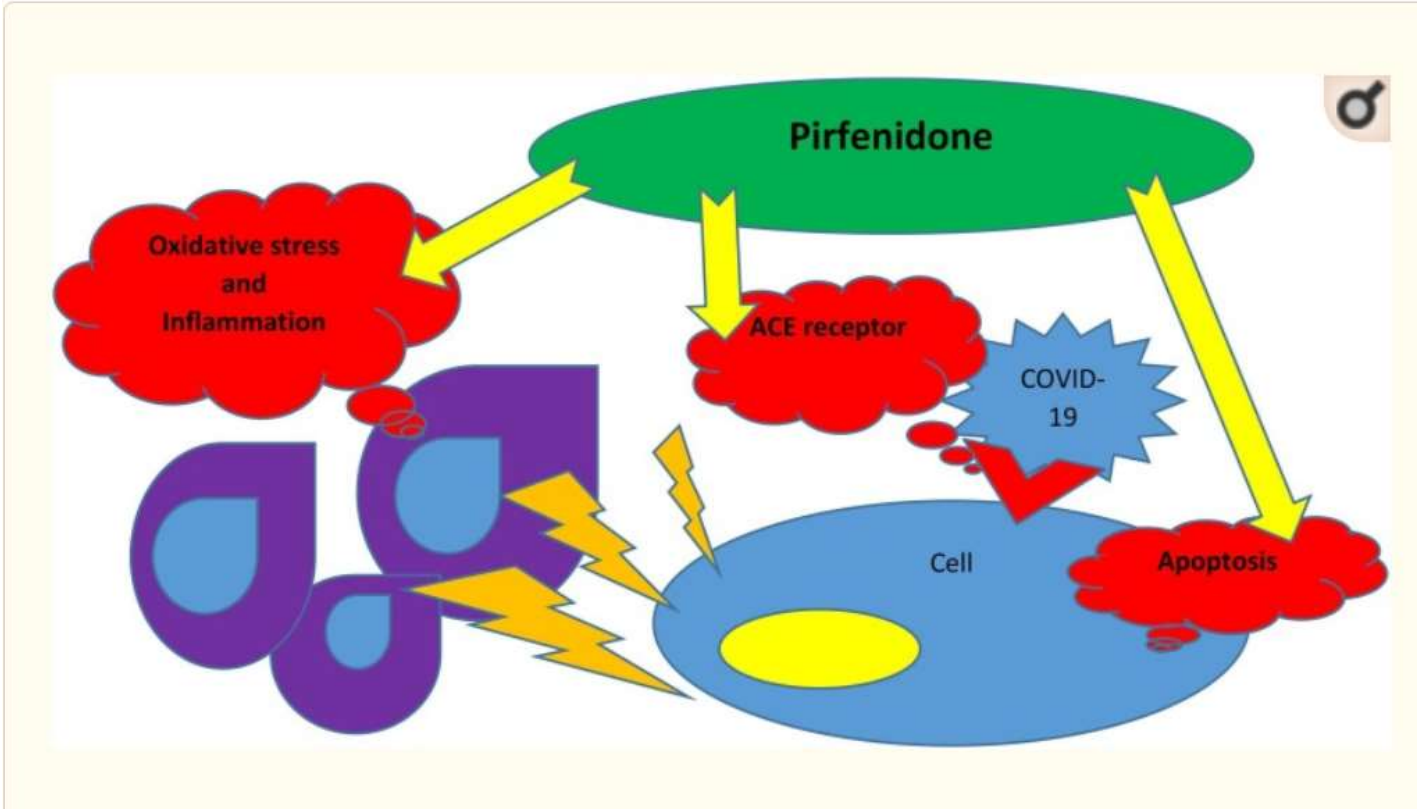
Fibrosis with fibroblasts and honeycombing has clearly been demonstrated in autopsies and explanted lungs of patients with SARS-C0V-2

Biological rationale for the use of both pirfenidone and nintedanib in COVID-ILD

known to inhibit experimental lung injury and inhibit IL-6, IL-1, and IL-1B

Pirfenidone has both antifibrotic and anti-inflammatory properties, inhibits the AT1R/p38 MAPK pathway, decreases angiotensin II, and angiotensin II type 1 receptor, as well as angiotensin-converting enzyme (ACE) expression

Vitiello A et al Lung India 2021;38:S129-30.



Soroush Seifirad et al .Front. Med. 7:625440

Pirfenidone in Covid 19 lung fibrosis

Both these antifibrotic drugs take at least 1–3 months to demonstrate an effect

Adding them at a late stage in patients already needing ventilator support may not be ideal

Giving these drugs to those who are spontaneously improving over time or whose fibrosis is static is unlikely to be useful

But , progression is difficult to ascertain when the patient is first seen and is only apparent over time

Identification of the subset of patients most likely to benefit from antifibrotic therapy a difficult task

Z F Udwadia et al.Lung India . Volume 38 . March 2021

Perspective

BMJ Open Respiratory Research

SARS-CoV-2 organising pneumonia: 'Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?'

Pierre Kory ,[1] Jeffrey P Kanne[2]

Viral-induced OP during the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and H1N1 viral pandemics have been well described

With SARS, OP and its histological variant, acute fibrinous and organising pneumonia (AFOP), were reported in 30%–60% of intensive care unit patients

The reported CT findings of COVID-19 suggest that secondary OP, AFOP or both may be occurring even more frequently.

Thus, the clinical course of COVID-19 and secondary OP tend to follow a subacute respiratory illness, although in both conditions a rapid-onset progression to fulminant respiratory failure and even death from extensive fibrosis has been described, with such cases reported to occur in approximately 5%–8% of secondary OP

Kory P, Kanne JP.*BMJ OpenRespRes*2020;**7**:e000724

Evidence of benefit with steroid

STUDY	DESIGN	STEROID TREATMENT	OUTCOME
Francesco Salton et al	Observational longitudinal study	Loading dose of 80 mg intravenously (iv) at study entry , followed by an infusion of 80 mg/d for at least 8 days, until achieving either a PaO2:FiO2 >350 mmHg or a CRP <20 mg/L; after that, oral administration at 16 mg or 20 mg iv twice daily until CRP reached <20% of the normal range or a PaO2:FiO2 >400	By day 28, the MP group had fewer deaths (6 vs 21; aHR , 0.29; 95% CI, 0.12–0.73) and more days off invasive MV (24.0 ± 9.0 vs 17.5 ± 12.8; *P* = .001).
RECOVERY	Open level RCT	In the dexamethasone group, 95% of the patients received at least one dose of a glucocorticoid. The median duration of treatment was 7 days (interquartile range, 3 to 10).	shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17)

Increasingly adopted RECOVERY trial protocol (6 mg dexamethasone daily for up to 10 days) may be insufficient given that treatment of secondary OP often requires higher doses, prolonged duration of treatment, and a careful and monitored tapering

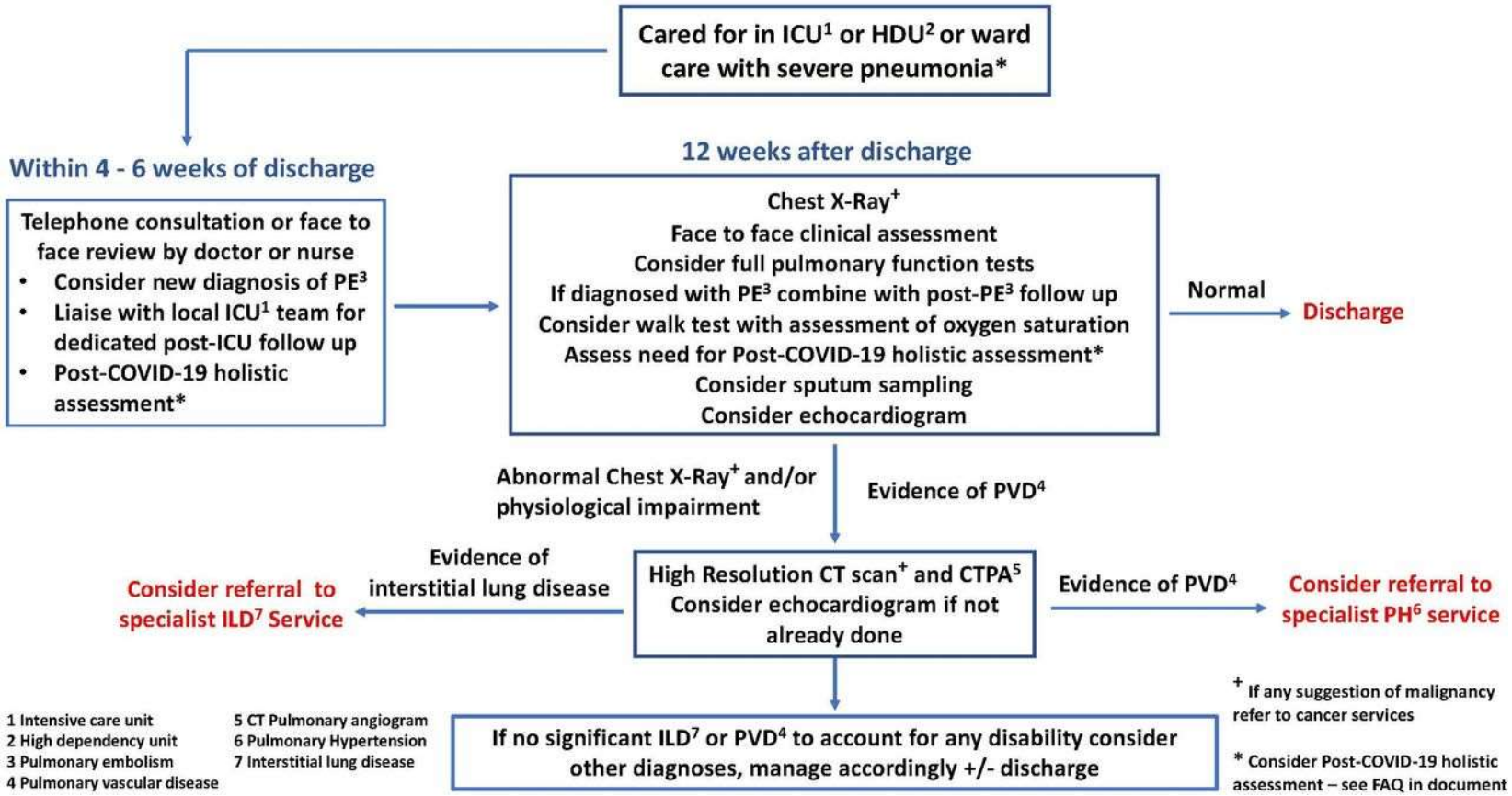
Kory P, Kanne JP.*BMJ OpenRespRes*2020;**7**:e000724

FOLLOW UP

As the ongoing presentation of pulmonary sequelae emerging, long term pulmonary follow up is suggested

Protocol adapted is different for different population as per initial presentation

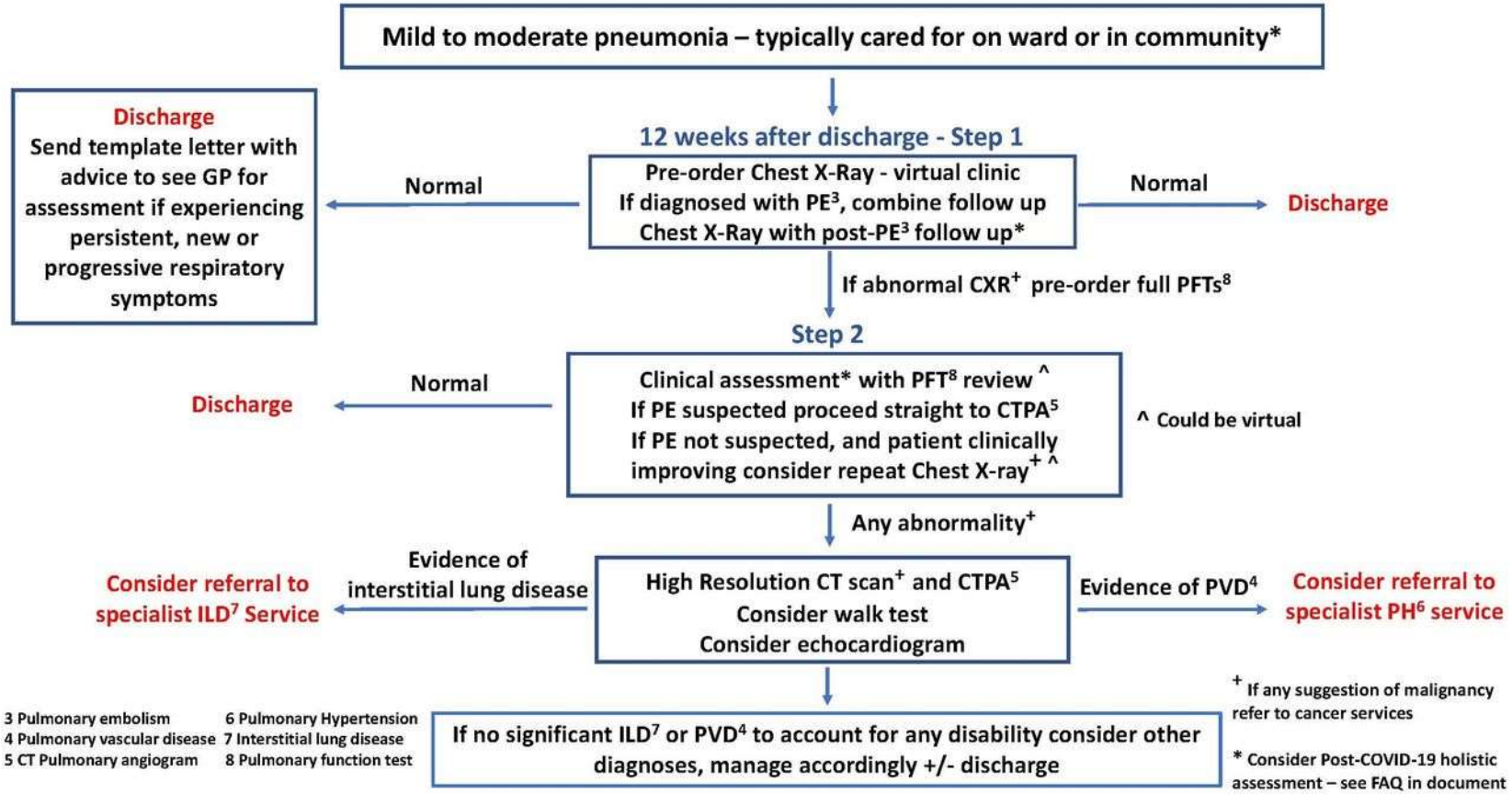
Respiratory follow-up algorithm for patients with COVID-19 pneumonia cared for in the ICU, HDU or those cared for on the ward with severe disease.



Peter M George et al. Thorax 2020;75:1009-1016

THORAX

Respiratory follow-up algorithm for patients with mild to moderate COVID-19 pneumonia– typically cared for on the ward or in the community.



Peter M George et al. Thorax 2020;75:1009-1016

ONGOING TRIALS

(ENDCOV-I)

The Study Will Evaluate the Use of Nintedanib in Slowing Lung Fibrosis in Patients With Pulmonary Infiltrates Related to COVID-19

Condition or disease	Intervention/treatment	Phase
Pulmonary FibrosisInterstitial Lung DiseaseRespiratory Disease	Drug: NintedanibDrug: Placebo	Phase 4

Study Type : Interventional (Clinical Trial)

Estimated Enrollment : 120 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Triple (Participant, Care Provider, Investigator)

Primary Purpose: Treatment

Official Title: Early Nintedanib Deployment in COVID-19 Interstitial Fibrosis

Actual Study Start Date : November 18, 2020

Estimated Primary Completion Date : July 2021

Estimated Study Completion Date : July 2021

Arm	Intervention/treatment
Experimental: Nintedanib150 mg po twice a day	Drug: Nintedanib150 mg PO twice a day, taken with food
Placebo Comparator: Placeboplacebo equivalent po twice a day	Drug: Placebo placebo equivalent given twice a day

Primary Outcome Measures :

Change in Forced Vital Capacity (FVC) [Time Frame: Baseline and 180 days]Change in Forced Vital Capacity (FVC) at 180 days as compared to baseline. Forced vital capacity (FVC) is the amount of air that can be forcibly exhaled from your lungs after taking the deepest breath possible, as measured by spirometry.

Treatment With Pirfenidone for COVID-19 Related Severe ARDS :An Open Label Pilot Trial

Condition or disease	Intervention/treatment	Phase
Covid19ARDS	Drug: PirfenidoneOther: Standard of care	Not Applicable

Study Type : Interventional (Clinical Trial)

Estimated Enrollment : 100 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Intervention Model Description: Following initial diagnosis of COVID-19, severe ARDS patient will be admitted to a dedicated intensive care unit (ICU) at Soroka University Medical Center (Day 0). Upon admission, patients will be randomized according to 1:1 ratio to one of the trial arms and receive either Pirfenidone 2,403mg administered through nasogastric tube as 801mg TID (intervention arm) plus SoC or SoC alone (control arm).

Masking: None (Open Label)

Primary Purpose: Treatment

Actual Study Start Date : November 8, 2020

Estimated Primary Completion Date : November 2021

Estimated Study Completion Date : December 2021

Outcome Measure

Primary Outcome Measures

1.Ventilation free days to day 28 (VFD28) [Time Frame: Up to 28 days from admission to ICU]
2.Severe adverse events (SAEs) rate [Time Frame: Through study completion, an average of 1 year]

Secondary Outcome Measures :

1.Mortality [Time Frame: Through study completion, an average of 1 year]
2.ICU length of stay [Time Frame: Through study completion, an average of 1 year]
3.Lung compliance [Time Frame: Through study completion, an average of 1 year]
4.Tidal Volume [Time Frame: Through study completion, an average of 1year].
5.PEEP[Through study completion , an average of one year]

6. Quality of life questionnaire [Time Frame: on admission and 6 months after discharge]Assessed by St George Respiratory Questionnaire (SGRQ).

7.Forced Vital Capacity (FVC) [Time Frame: On admission (if possible) and 6 months after discharge]

8.Forced Expiratory Volume at first second (FEV1) [Time Frame: On admission (if possible) and 6 months after discharge]

9.6 minutes walking test [Time Frame: 6 months after discharge from hospital]

FIBROCOVID
PIRFENIDONE COMPARED TO PLACEBO IN POST COVID19 PULMONARY FIBROSIS

Condition or disease	Intervention/treatment	Phase
Fibrotic Pulmonary Sequelae Post-COVID19 Infection	Drug: PirfenidoneDrug: Placebo	Phase 2

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	:148 participant
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model :	2:1 (treatment: placebo)
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Prevention
Official Title:	Phase-II Randomized Clinical Trial to Evaluate the Effect of Pirfenidone Compared to Placebo in Post-COVID19 Pulmonary Fibrosis
Actual Study Start Date :	August 1, 2020
Estimated Primary Completion Date :	August 1, 2021
Estimated Study Completion Date :	August 1, 2021

Arm	Intervention/treatment
Placebo Comparator: Placebo No anti-fibrotic treatment. Patients in placebo and treatment arm may be on corticosteroid treatment	Drug: Placebo.Comparing the effect of pirfenidone in avoiding establishing or progression of fibrosis induced after COVID19 infection
Experimental: Treatment Pirfenidone	Drug: Pirfenidone.Comparing the effect of pirfenidone in avoiding establishing or progression of fibrosis induced after COVID19 infection

Primary Outcome Measures :

To investigate the effect of pirfenidone administered for 24 weeks measuring the number of patients who have pulmonary fibrotic changes from baseline after suffering severe COVID19 pneumonia, analysed by

- Change From Baseline in % in forced vital capacity (FVC)
- Change From Baseline % fibrosis in high resolution computed tomography (HRCT) of the lung

Secondary Outcome Measures :

1.Maintenance of stability or functional improvement FVC [Time Frame: 24 weeks]

2.Decreased oxygen requirement for physical activity [Time Frame: 24 weeks]

3.Improved exercise capacity (> 50 meter improvement or less decrease in% oxygen saturation) in the 6 min walk test[Time Frame: 24 weeks]

4.Hospitalizations (general and due to respiratory problems) [Time Frame: 24 weeks]

5.Visits to the Emergency or Day Hospital for respiratory causes
[Time Frame: 24 weeks]

6.Lung transplantation [Time Frame: 24 weeks]

7.Death [Time Frame: 24 weeks]

- Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis (NINTECOR)

Condition/Disease	Intervention/treatment	Phase
SARS-Cov-2 Induced Pulmonary Fibrosis	Drug: Nintedanib 150 MG [Ofev]Other: Placebo	Phase 3

www.clinicaltrial.gov

Study Type	: Interventional (Clinical Trial)
Estimated Enrollment	: 250 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Treatment
Official Title:	"Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis"
Actual Study Start Date	: October 29, 2020
Estimated Primary Completion Date	: March 2021
Estimated Study Completion Date	: December 2021

Arm	Intervention/treatment
Experimental: NintedanibExperimental group will receive nintedanib 150mg BID for 12 months in addition to standard of care (SoC). Nintedanib dose could be reduced to 100mg BID depending on tolerance according to investigator in charge of the patient. The prescription of SoC drugs or procedure will be let to the choice of the investigator in charge of the patient.	Drug: Nintedanib 150 MG [Ofev]Experimental group will receive nintedanib 150mg BID for 12 months in addition to standard of care (SoC). Nintedanib dose could be reduced to 100mg BID depending on tolerance according to investigator in charge of the patient. The prescription of SoC drugs or procedure will be let to the choice of the investigator in charge of the patient.
Placebo Comparator: PlaceboControl group will receive Placebo BID for 12 months in addition to SoC. The prescription of SoC drugs or procedure will be let to the choice of the investigator in charge of the patient. Standard of care may include pulmonary rehabilitation.	Other: Placebo Other Name: NaCl

Primary Outcome Measures :

1.The primary objective is to assess whether nintedanib slows the progression of lung fibrosis in COVID-19 survivors as assessed by the decline in the forced vital capacity (FVC) over 12 months compared to placebo. [Time Frame: at inclusion and 12 months.]

Change in Forced Vital Capacity over 12 months assessed by Annual Rate of Decline in FVC in Overall Population

Secondary Outcome Measures

1.compare the rate of decline of DLCO over 12 months [Time Frame: at inclusion, 6 and 12 months]

2.compare exercise capacity at 12 months [Time Frame: at 12 months]

3.compare high resolution CT (HRCT) lung opacities extension at 12 months
[Time Frame: at inclusion and 12 months]

4.compare change in health-related quality of life [Time Frame: at 12 months]

5.compare the evolution of dyspnea over time [Time Frame: at 3, 6, 9 and 12 months]

6.compare change in Depression and anxiety over time [Time Frame: at 3, 6, 9 and 12 months]

7.compare change in lung injury, pulmonary hypertension and inflammation biomarkers [Time Frame: at inclusion and 12 month]

8.pulmonary hypertension prevalence at inclusion and 12 months [Time Frame: at inclusion and 12 months]

9.association between genetic susceptibility (MUC5B polymorphism) and lung fibrosis in COVID-19 survivors [Time Frame: at inclusion]

10.safety of nintedanib [Time Frame: over 12 months]

- **Oral Prednisone Regimens to Optimize the Therapeutic Strategy in Patients With Organizing Pneumonia Post-COVID-19 (NORCOVID)**

Condition or disease	Intervention/treatment	Phase
COVID-19 Pneumonia	Drug: Prednisone	Phase 4

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	120 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Parallel clinical trial with therapeutic intervention, randomized, open and controlled, of non-inferiority
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Randomized, Open, Parallel, Single-center, Non-inferiority Clinical Trial, With an Active Control Group, Comparing Two Oral Prednisone Regimens With the Aim of Optimizing the Therapeutic Strategy in Patients With Organizing Pneumonia Post-COVID-19 Infection
Estimated Study Start Date :	September 7, 2020
Estimated Primary Completion Date :	May 2, 2021
Estimated Study Completion Date :	December 15, 2021

Arm	Intervention/treatment
Active Comparator: Control GroupPrednisone 0.75mg / Kg / d 4 weeks; 0.5mg / Kg / d 4 weeks; 20mg / d 4 weeks; 10mg / d 6 weeks; 5mg / d 6 weeks (6m)	Drug: Prednisone Patients will be randomized 1: 1 between the two arms of the study
Active Comparator: Experimental groupPrednisone 0.5mg / Kg / d 3 weeks, 20mg / day 3 weeks; 15mg / day 2 weeks; 10mg / day 2 weeks, 5mg / day 2 weeks and discontinue.	Drug: Prednisone Patients will be randomized 1: 1 between the two arms of the study

Primary Outcome Measures :

Change in pulmonary diffusion. [Time Frame: Six Months] in terms of predicted DLCO (%)

- **Comparison of Two Corticosteroid Regimens for Post COVID-19 Diffuse Lung Disease (COLDSTER)**

CONDITION	INTERVENTION/TREATMENT	PHASE
Post COVID 19 diifuse lung disease	Drug:Medium dose prednisolone Drug:Low dose prednisolone	Not applicable

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	100 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Comparison of the Efficacy and Safety of Two Corticosteroid Regimens in the Treatment of Diffuse Lung Disease After Coronavirus Disease 2019 (COVID-19) Pneumonia
Actual Study Start Date :	December 8, 2020
Estimated Primary Completion Date :	December 7, 2021
Estimated Study Completion Date :	December 7, 2021

Arm	Intervention/treatment
Active Comparator: Medium dose prednisolone An initial dose of 40 mg/day will be administered for 1 week, followed by 30 mg/day for 1 week, 20 mg/day for 2 weeks, 10 mg/day for 2 weeks	Drug: Medium dose prednisoloneSame as arm description
Active Comparator: Low dose prednisoloneA dose of 10 mg/day of prednisolone will be administered for 6 weeks	Drug: Low dose prednisolone.Same as arm description

Primary Outcome Measures ：

1.Proportion of subjects with a complete radiologic response
[Time Frame: 6 weeks]
Complete response is defined as complete disappearance or ≥90% reduction in the lung parenchymal abnormalities on a high-resolution CT scan

Secondary Outcome Measures ：

1.Proportion of subjects with a complete or good response radiologic response [Time Frame: 6 weeks]Complete response is defined as complete disappearance or ≥90% reduction in the lung parenchymal abnormalities on a high-resolution CT scan. Good response is defined as ≥50% but less than 90% reduction in the lung parenchymal abnormalities on a high-resolution CT scan.

2.Proportion of subjects with a good composite response [Time Frame: 6 weeks]Complete or good radiologic resolution along with no oxygen desturation on exercise testing

3.Forced vital capacity as a percentage of the predicted [Time Frame: 6 weeks]

4.Change in resting oxygen saturation [Time Frame: 6 weeks]

5.Proportion of subjects with oxygen desaturation on exercise testing [Time Frame: 6 weeks]

6.Change in dyspnea score [Time Frame: 6 weeks]

7.Severity of dyspnea [Time Frame: 6 weeks]

8.Respiratory health status [Time Frame: 6 weeks]

9.Health-related quality of life [Time Frame: 6 weeks]

10.Adverse effects of prednisolone [Time Frame: 6 weeks]

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Inclusion Criteria:

Diagnosed to have COVID-19 by means of a real-time reverse transcription polymerase chain reaction (rRT-PCR) test performed on a respiratory (upper or lower respiratory) sample or the detection of COVID-19 antigen)

Having significant respiratory symptoms (cough and breathlessness) or persistent hypoxemia or oxygen desaturation on exercise and CT chest showing residual changes of post-COVID parenchymal involvement of any extent OR having CT chest showing residual changes of post-COVID parenchymal involvement >20% of the lung parenchyma on visual inspection of the scans between 3-8 weeks of the onset of symptoms of COVID-19

Willing to participate in the study

Exclusion Criteria:

Receiving ventilatory or respiratory support (invasive or non-invasive mechanical ventilation or high flow nasal cannula) or supplemental oxygen with $FiO_2 > 0.35$

Requiring intensive care due to acute COVID-19 pneumonia or its complications

Having a known lung parenchymal lung disease before the onset of COVID-19

Pregnant or lactating women

Having absolute contraindication for prednisolone in a dose of 40 mg/day (this includes untreated glaucoma, uncontrolled diabetes mellitus, signs of an uncontrolled or untreated infection or sepsis, pulmonary mycosis, untreated severe psychiatric disorders)

Unwilling to provide informed consent

Ongoing trials on Anticoagulation

Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19 (COVID-PREVENT)

Condition or disease	Intervention/treatment	Phase
COVID-19	Drug: RivaroxabanOther: Standard Of Care (SOC)	Phase 3

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	400 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	A multicenter, prospective, randomized, event-driven study.
Masking:	None (Open Label)
Primary Purpose:	Prevention
Official Title:	Effect of Anticoagulation Therapy on Clinical Outcomes in Moderate to Severe Coronavirus Disease 2019 (COVID-19)
Actual Study Start Date :	November 30, 2020
Estimated Primary Completion Date :	April 30, 2021
Estimated Study Completion Date :	May 30, 2021

Arm	Intervention/Treatment
Experimental: RivaroxabanSubjects will receive treatment with rivaroxaban. (for more information see intervention description)	Drug: Rivaroxaban Treatment with Rivaroxaban 20 mg (15 mg for subjects with an eGFR ≥30 mL/min/1.73m2 and <50 mL/min/1.73m2) once daily (OD) for at least 7 days. In case of hospitalization for more than 7 days, the therapeutic treatment with rivaroxaban will be continued for the duration of the hospital stay until discharge. Post discharge patients randomized to the rivaroxaban study arm(with no other indication of thromboprophylaxis) will receive reduce daily dosage to 10 mg OD. Thromboprophylaxis therapy will be given for 28 days up to day 35 post randomization or even longer
Standard of CareSubjects will receive standard of care (SOC) treatment SOC including prophylactic LMWH or UFH, when considered appropriate according to the judgment of the treating physician.	Other: Standard Of Care (SOC)Standard of care treatment

Outcome Measures

Primary Outcome Measures ：

1.Composite endpoint of venous thromboembolism (DVT and/or fatal or non-fatal PE), arterial thromboembolism, new myocardial infarction, non-hemorrhagic stroke, all-cause mortality or progression to intubation and invasive ventilation [Time Frame: 35 days post randomization]

Secondary Outcome Measures :

1.Development of disseminated intravascular coagulation (DIC) according to the ISTH criteria [Time Frame: 35 days post randomization]

2.Number of days requiring invasive ventilation [Time Frame: 35 days post randomization]

3.Number of days requiring non-invasive ventilation [Time Frame: 35 days post randomization]

4.Improvement on a seven-category ordinal scale recommended by the WHO as clinical improvement scale for patients with respiratory infections
[Time Frame: 35 days post randomization]

www.clinicaltrials.gov

TAKE HOME MESSAGE

Listen to your patient; he is telling you the diagnosis

William Osler

Follow up for persistent symptoms

Universally acceptable management protocol yet to come

Individualized management protocol need of the hour

THANK YOU