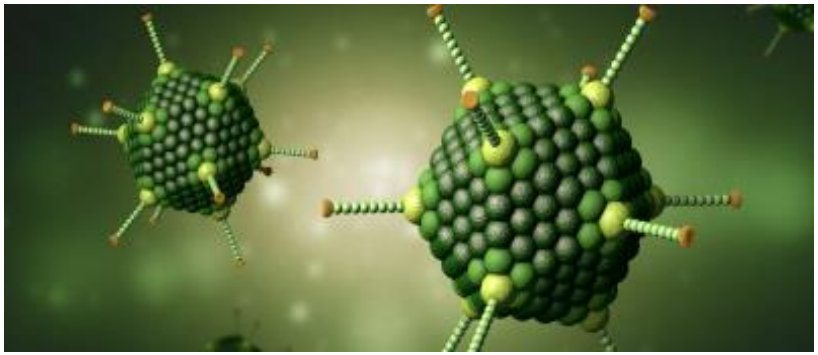
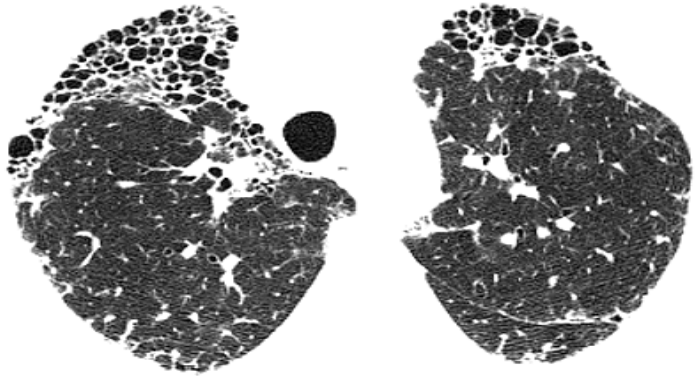
Idiopathic pulmonary fibrosis in view of COVID19 pandemic

Demosthenes Bouros *MD, PhD, FERS, FCCP, FAPSR*
Professor of Pneumonology
University of Athens, Greece
dbouros@med.uoa.gr

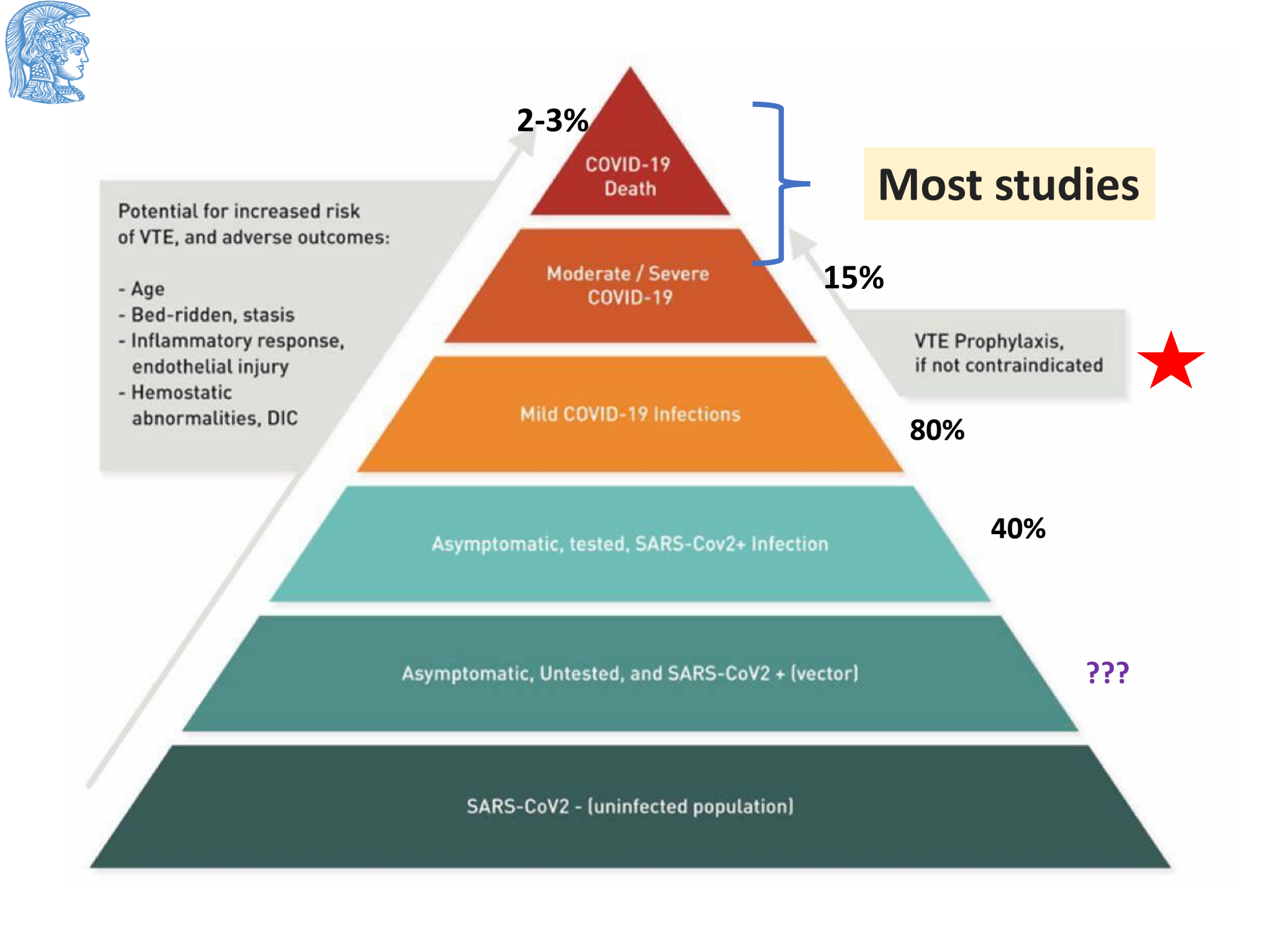




SARS-CoV-2 OVERVIEW

In December 2019, a novel coronavirus, was detected as an etiologic agent of Severe Acute Respiratory Syndrome named SARS-coronavirus 2 (SARS-CoV-2) with the potential of multiorgan involvement, named Corona Virus Disease-2019 (COVID-19), easily transmissible through respiratory routes.

Around 5% of patients with COVID-19 develop critical manifestations, such as ARDS, PE, cardiac and septic shock and multiple organ failure necessitating ICU support. Mortality for those admitted in the ICU ranges from 40% to 60%.


2-3%
COVID-19
Death
Most studies
Potential for increased risk
of VTE, and adverse outcomes:
- Age
- Bed-ridden, stasis
- Inflammatory response,
endothelial injury
- Hemostatic
abnormalities, DIC
Moderate / Severe
COVID-19
15%
VTE Prophylaxis,
if not contraindicated
Mild COVID-19 Infections
80%
Asymptomatic, tested, SARS-Cov2+ Infection
40%
Asymptomatic, Untested, and SARS-CoV2 + (vector)
???
SARS-CoV2 - (uninfected population)

JAMA editor
2020- A year to be remembered!

2020 may be a transformative year of the 21st century.

The worst pandemic since 1918

Pubmed>50.000 papers!

Lessons from the classic Greek tragedies: Sophocles
The borders of medicine in the middle of pandemic.

Eugene-Ernest Hillemacher (1818-1887), Oedipus and Antigone Exiled From Thebes, circa 1843. Musée des Beaux-Arts, Orleans

Ryan Antiel, MD. JAMA Published online May 21, 2020

“What do you have to lose? Take it.”

President proposes ultraviolet light, injection of cleaning agents and chloroquine, as methods to kill virus!

- **KUNG FLU!**

Trump Disagrees With Top Immunologist Antony Fauci, Over Untested Drug Treatment for Covid-19

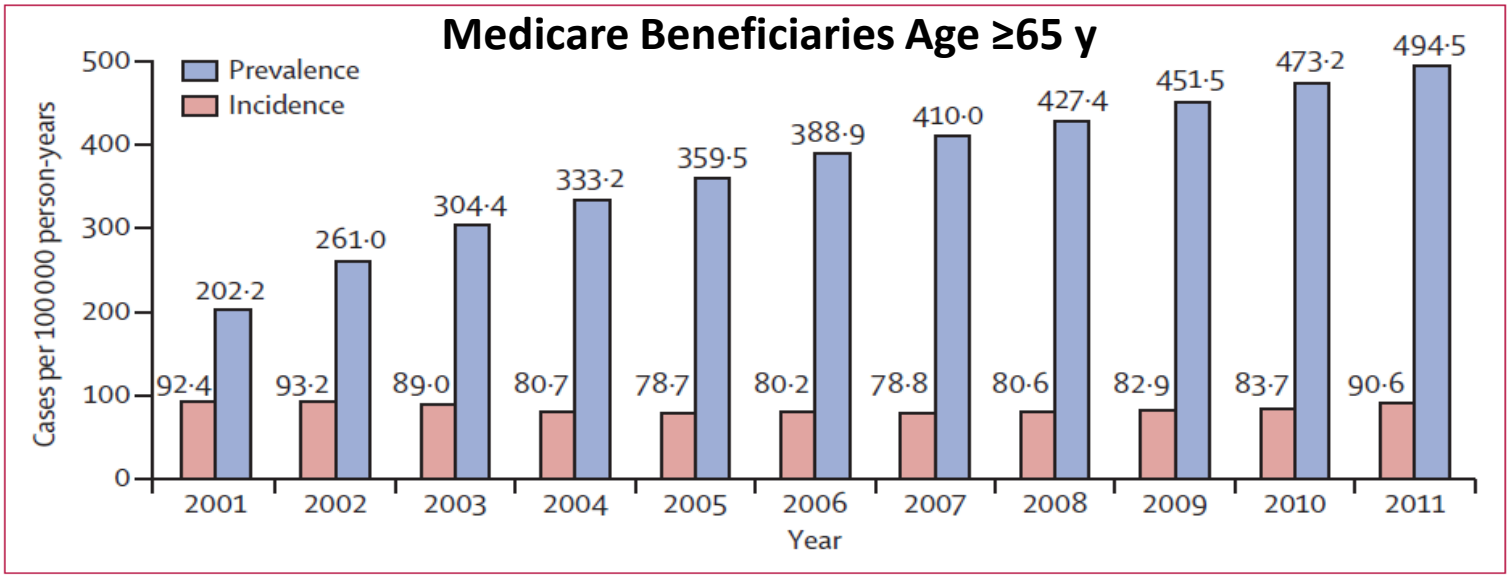
The need for RCTs

- According to the Cochrane COVID-19 Study Register as of April 28, there are 854 interventional trials registered.
- GCP was developed to protect the rights, safety, and welfare of humans participating in research.
- Without a control group, we can never, ever safely find new medications for any disease,“
- Lesson of the 2014 Ebola outbreak, in which 30,000 individuals were infected and numerous therapies were tested, but no new drugs emerged.

IPF OVERVIEW

IPF is an irreversibly progressive diffuse lung disease characterized by a usual interstitial pneumonia pattern (UIP). IPF presents with an ominous prognosis with a median survival of around five years. The development of ARDS during its clinical course, still defined IPF acute exacerbation (AE), represents the most devastating of its complications leading to death in a few days in almost all patients. Viral infections upon an altered lung hosted microbiome constitute the most important triggering factor of IPF /AEs.

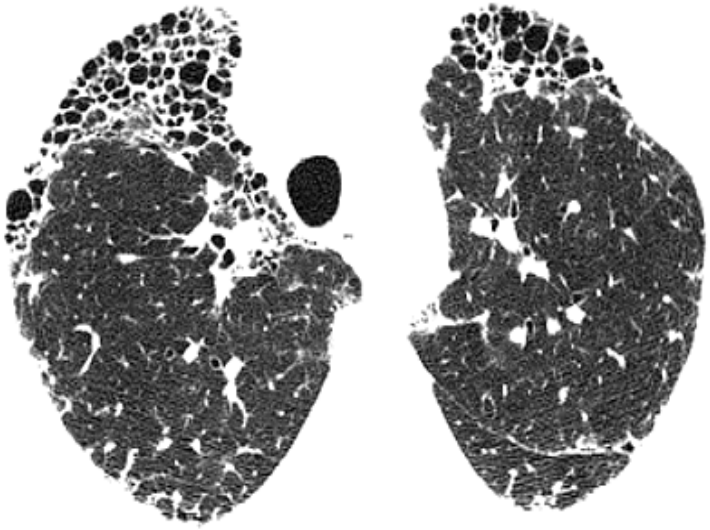
Increasing Prevalence of idiopathic Pulmonary Fibrosis



Factors associated with lower survival:
Age, index year, male gender

Median survival = 3.8 y

Raghu G, et al. *Lancet Respir Med*. 2014;2:566-572.



Typical UIP/IPF Honeycombing

- characteristic cystic appearance
- ~ 1 cm diameter (mm-cm)
- clearly definable walls (1-3 mm thickness)
- adjacent cysts share walls

IPF Comorbidities

Pulmonary	Extra-Pulmonary
Pulmonary hypertension	Gastroesophageal reflux disease
Obstructive sleep apnea	Coronary artery disease
Lung cancer	Heart failure
	Thromboembolic disease
	Diabetes

THE CHALLENGE

COVID-19 means that people with ILD face new health challenges.

To meet the need from the members to overcome the challenges many ILD centers plan virtual medical lectures for 2020

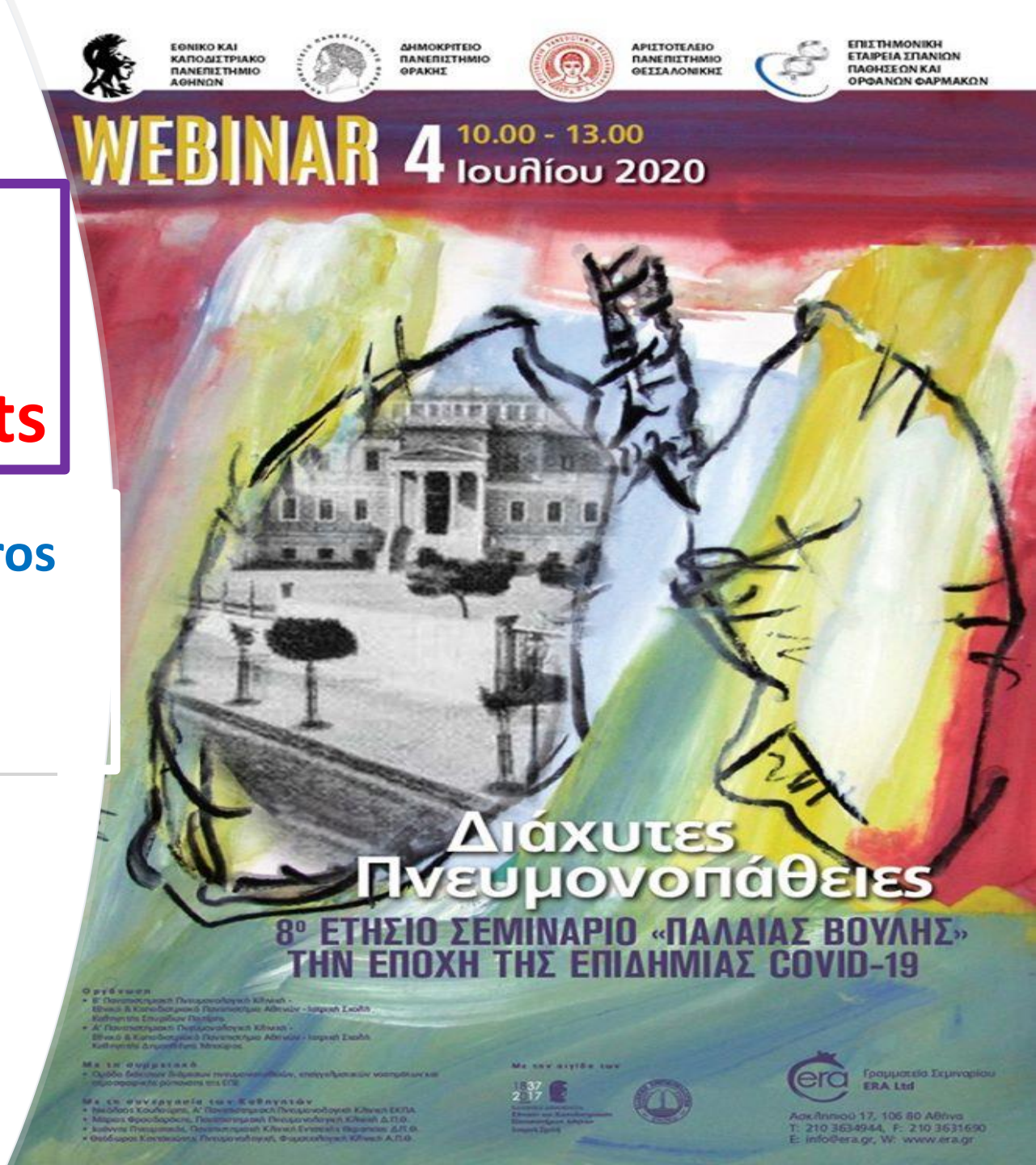
Treatment in COVID-19: facts and faults

Demosthenes Bouros

MD, PhD, FERS, FCCP, FAPSR

Emeritus Professor

University of Athens



WEBINAR
8ο ΕΤΗΣΙΟ ΣΕΜΙΝΑΡΙΟ «ΠΑΛΑΙΑΣ ΒΟΥΛΗΣ» ΤΗΝ ΕΠΟΧΗ ΤΗΣ ΕΠΙΔΗΜΙΑΣ COVID-19
Διάχυτες Πνευμονοπάθειες
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4 Ιουλίου 2020

IPF IS A HIGH-RISK DISEASE FOR COVID-19

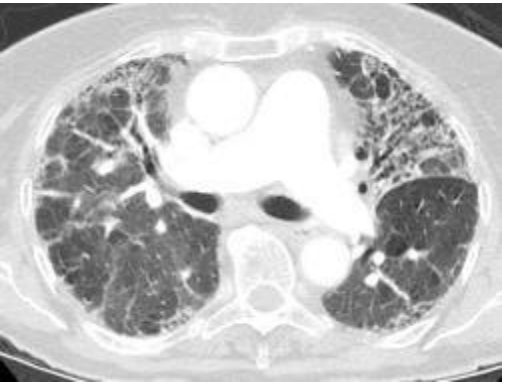
- **Older people with chronic comorbidities are at higher risk for developing serious illness from SARS-CoV-2, including those with IPF.**
- **Patients with IPF, are older, have multiple comorbidities.**
- **The higher risk category should reduce the risk of being exposed to SARS-CoV-2.**
- **Currently, there is no data regarding the incidence of COVID-19 in the field of ILDs.**

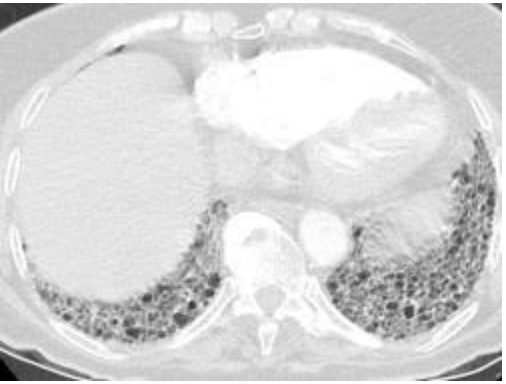
Infection *vs*. exacerbation of IPF

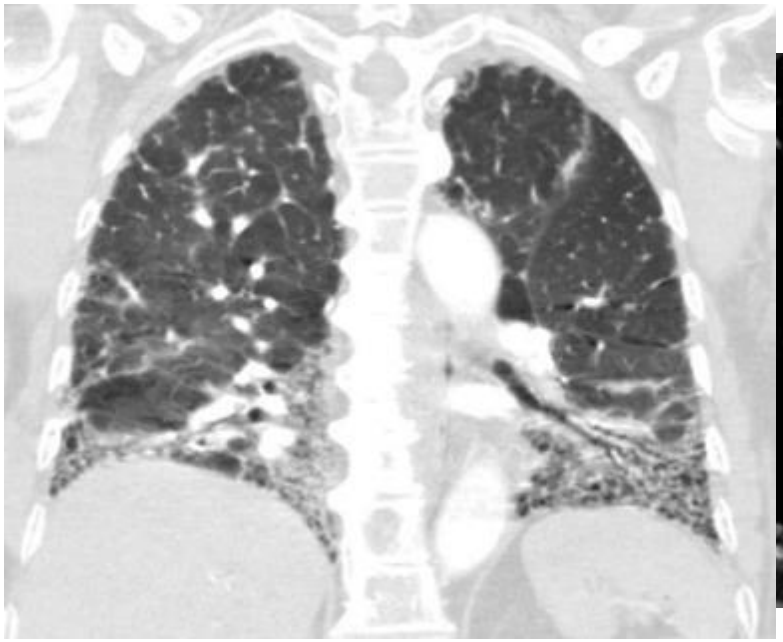
August

October

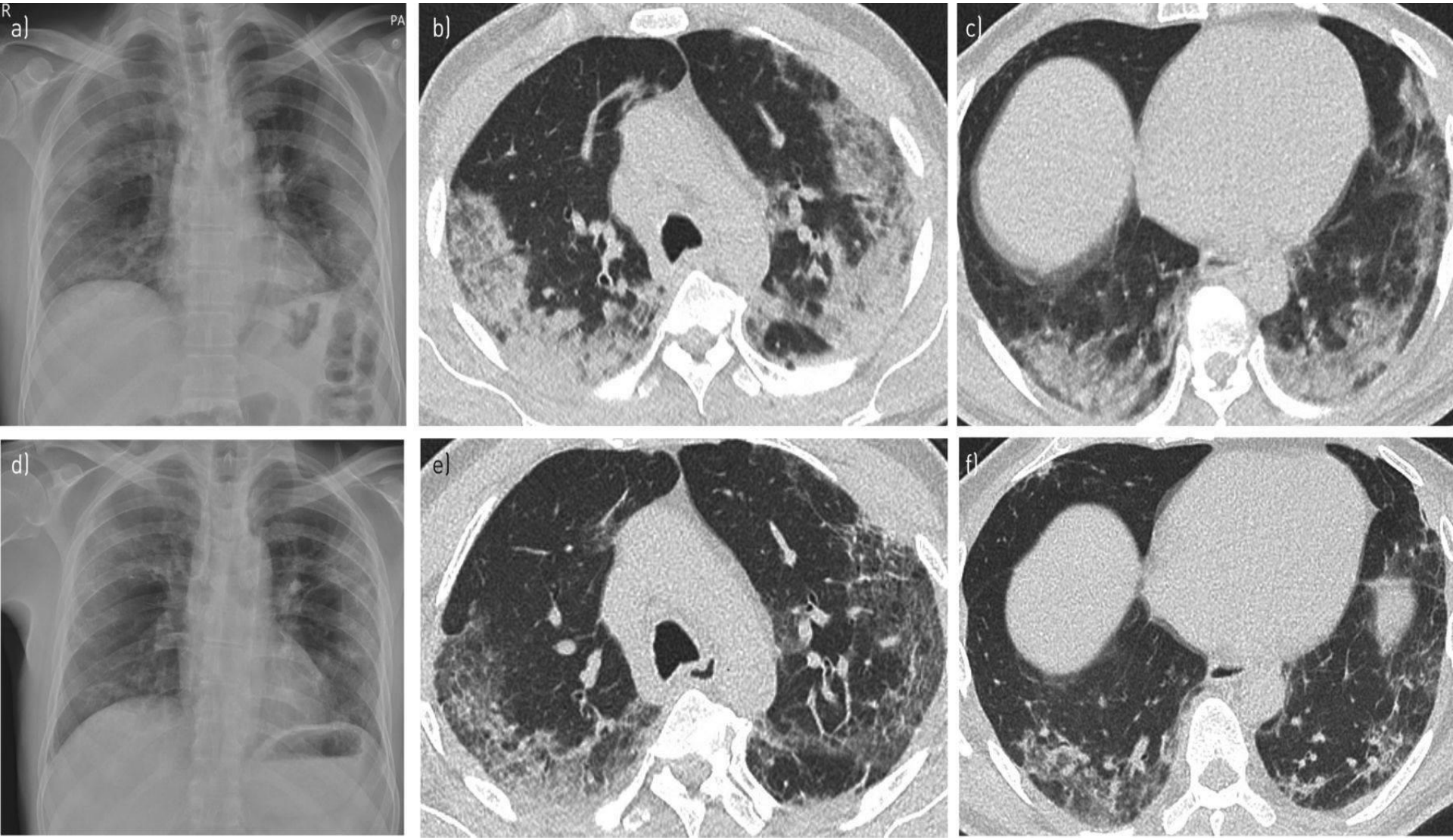
UIP/IPF and PE







CXR AND HRCT IN COVID-19



Pulmonary fibrosis secondary to COVID-19: a call to arms?

*Paolo Spagnolo, Elisabetta Balestro, Stefano Aliber
Elisabetta Cocconcelli, Davide Biondini, Giovanni De
Nicola Sverzellati, Toby M Maher

At present, the long-term pulmonary consequences of COVID-19 remains speculative and should not be assumed without appropriate prospective study.

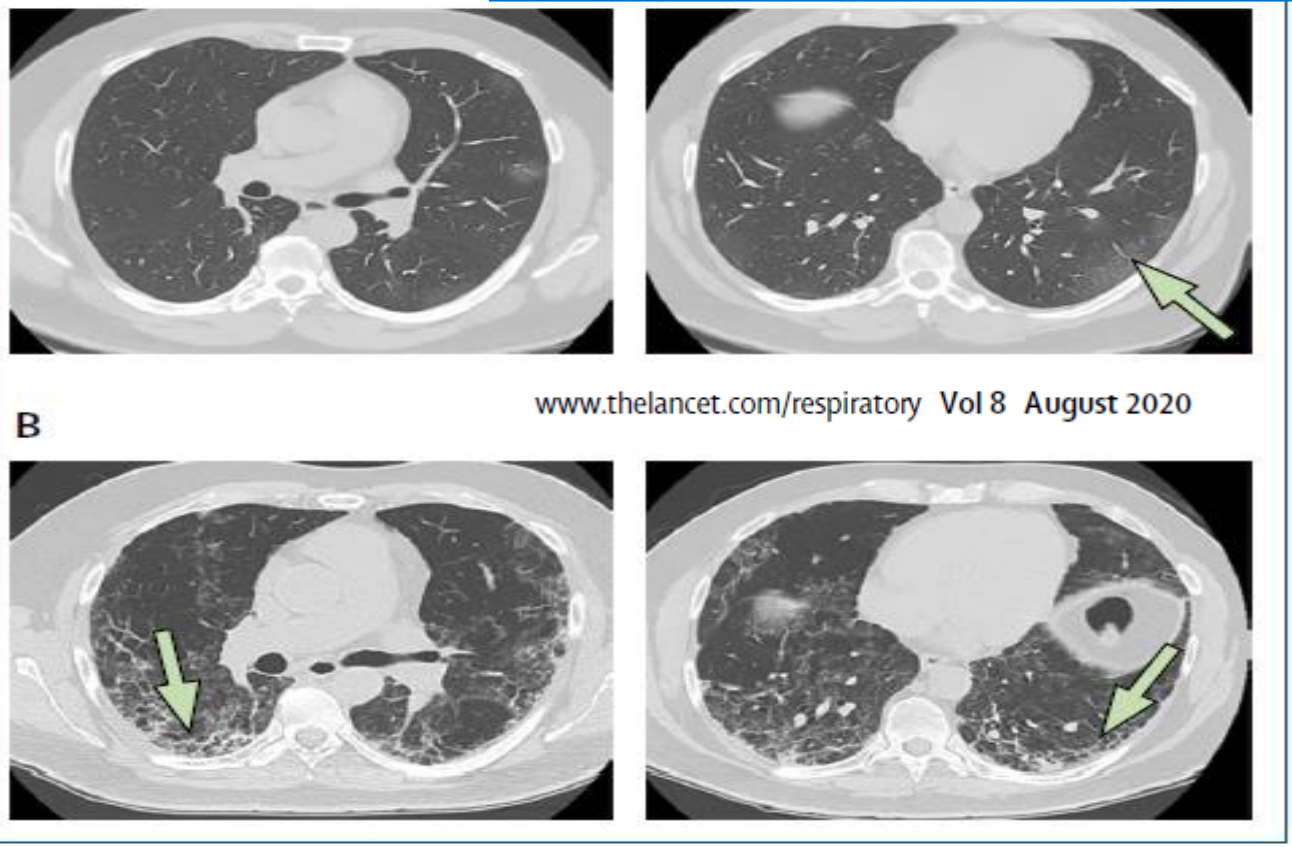


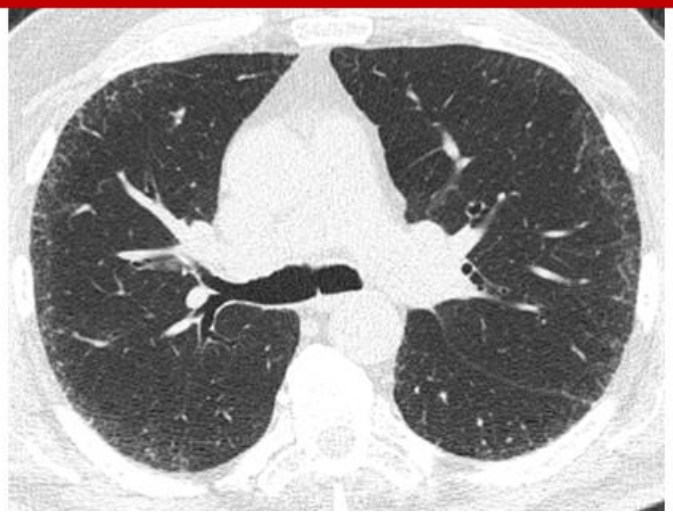
Figure: **Lung CT of a patient with coronavirus disease 2019**
(A) Images of peripheral mild ground glass opacities in the left lower lobe (arrow). (B) Three weeks later, at the same lung zones, the disease has rapidly progressed and fibrotic changes are now evident (arrows).

HRCT IN A COVID-19 PATIENT

Male, 72

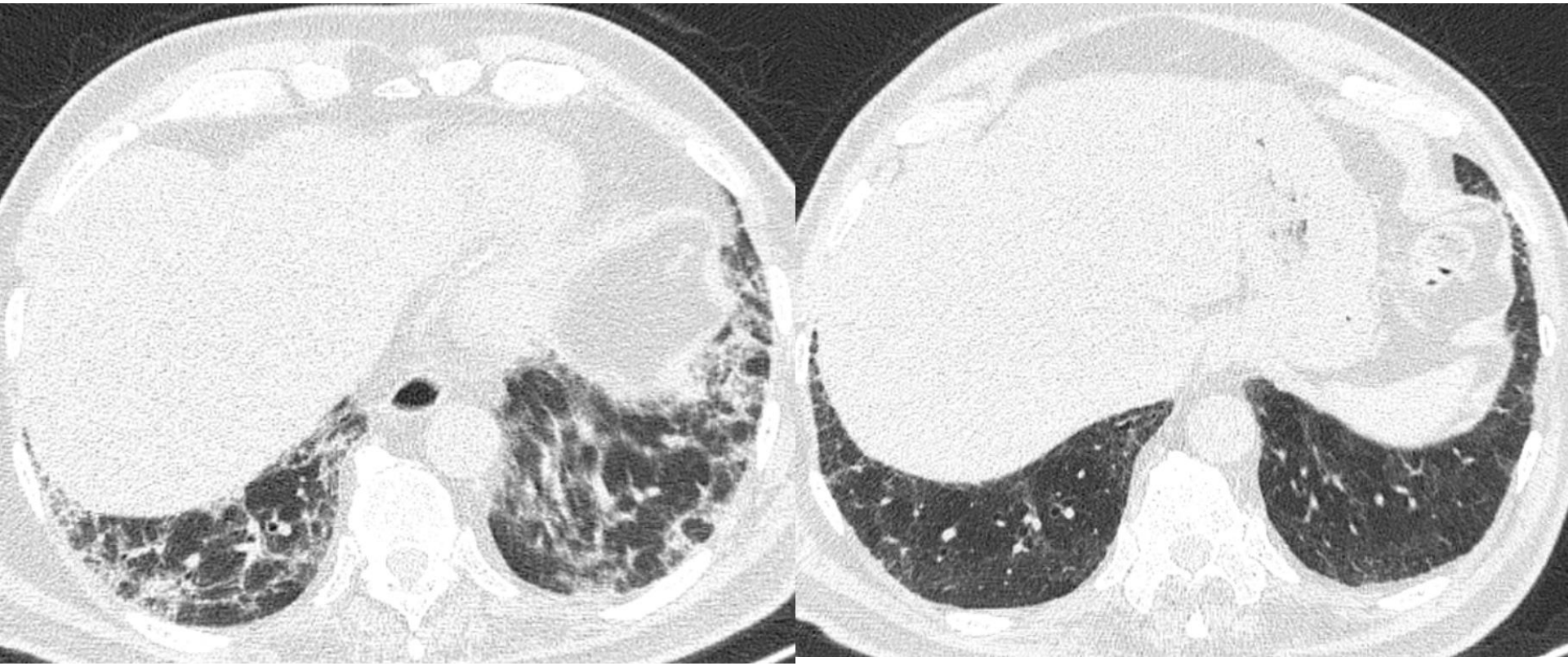
Male, 72

After 2 months

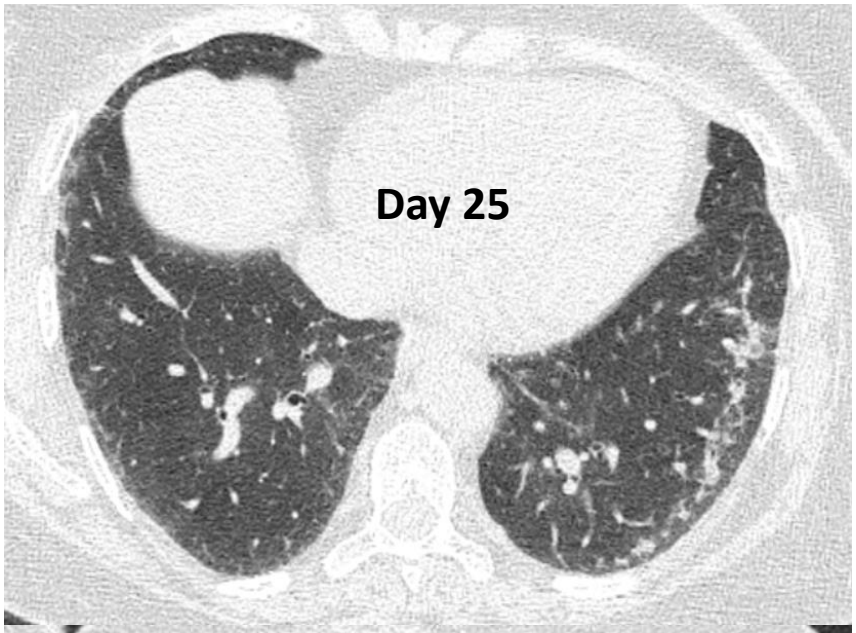


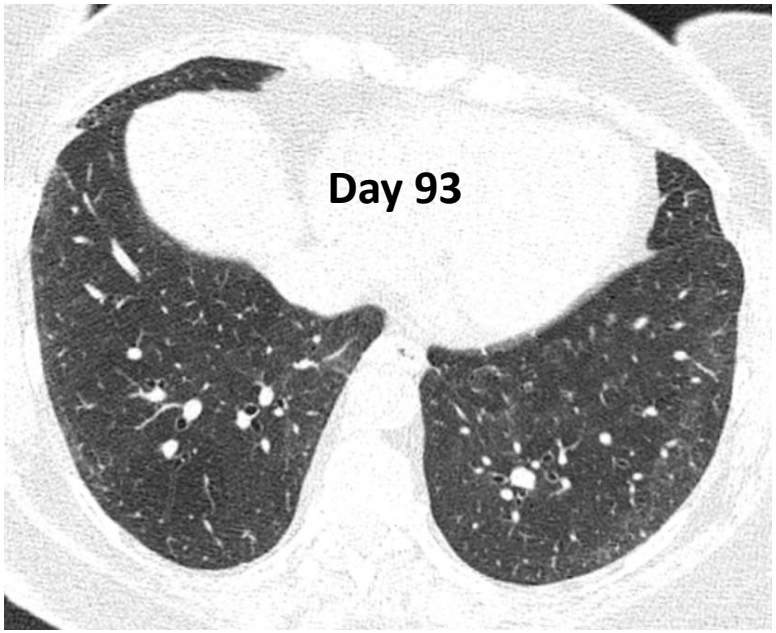
After 2 months

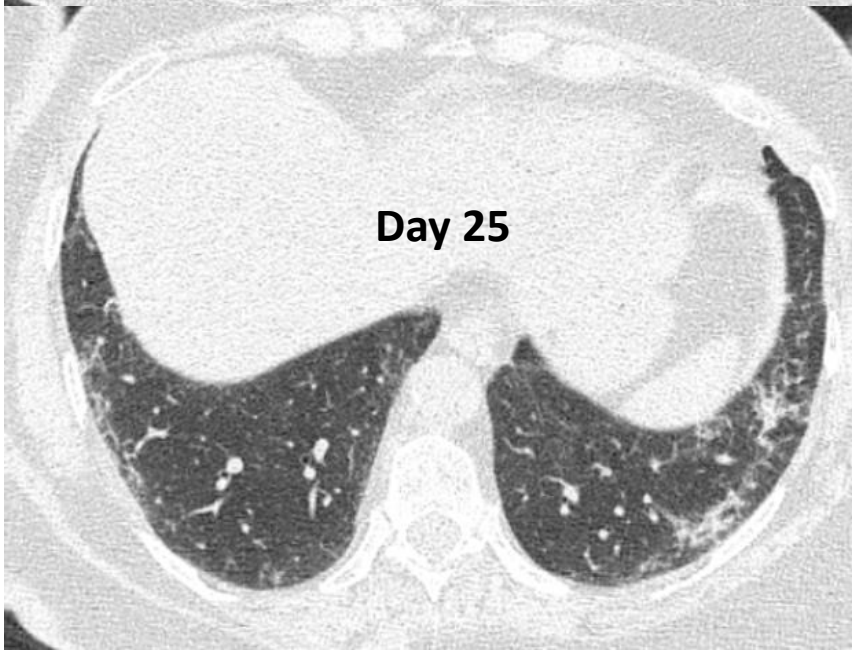
Evolution over 68 days

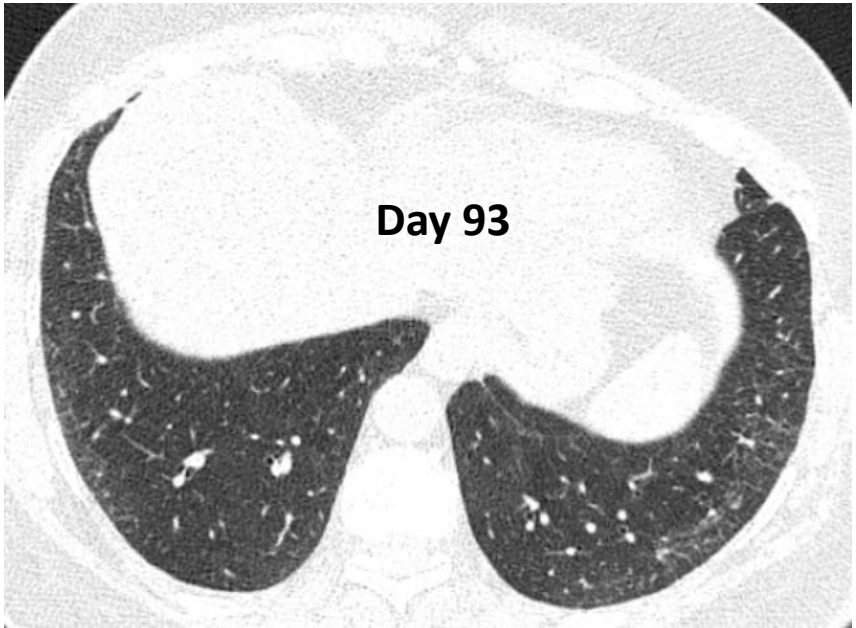


Female, 69



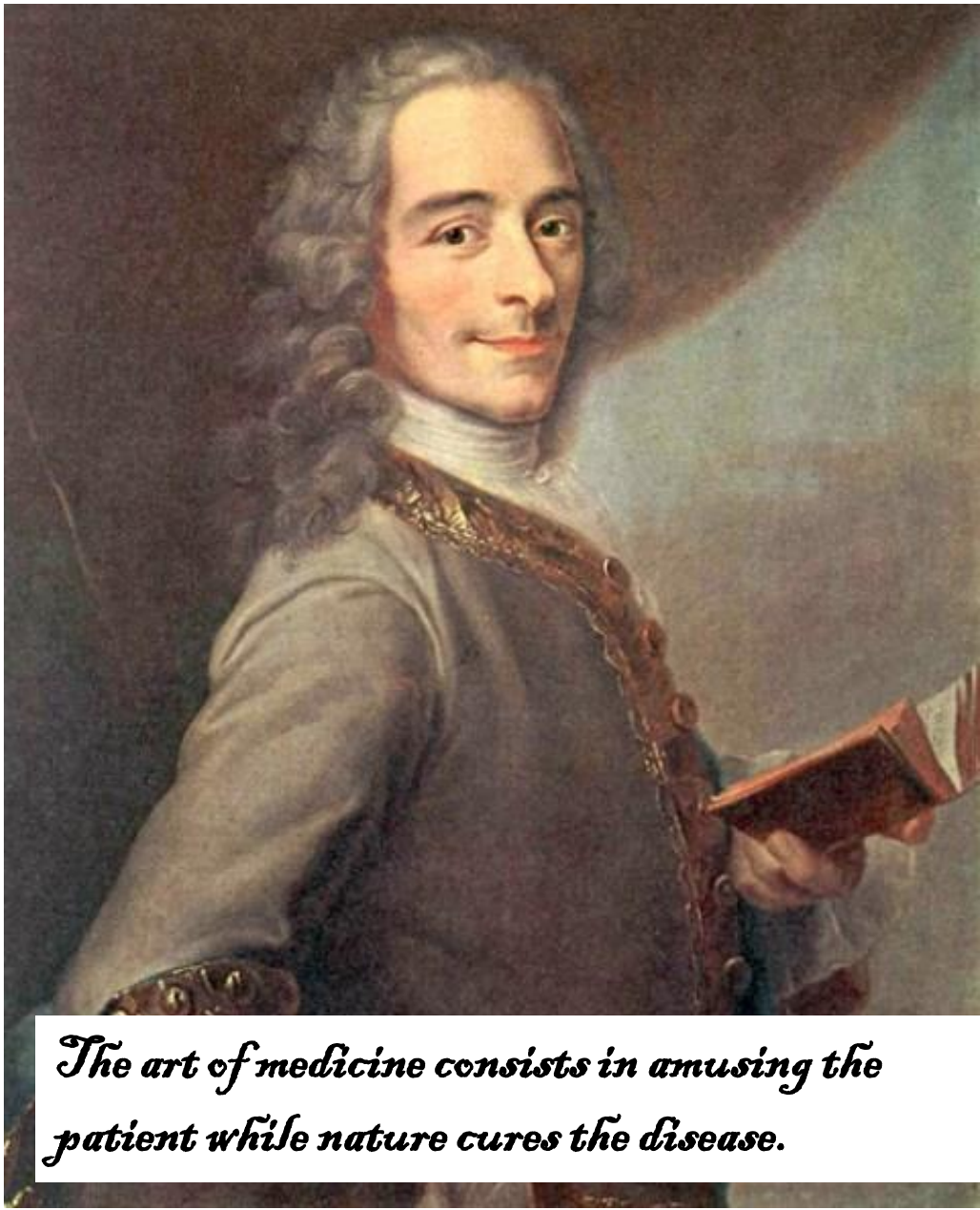






What was the treatment?

- Steroids
- Colchicine
- Remdesivir
- Tocilizumab
- Antifibrotics
- None of the above



The art of medicine consists in amusing the patient while nature cures the disease.

Increased Odds of Death for Patients with ILD and COVID-19: *A Case-Control Study*

- ✓ **Patients with ILD who contracted COVID-19 had a > four-fold increased death,**
- ✓ **were more likely to be hospitalized and require ICU care,**
- ✓ **and were less likely to be discharged,**

compared to a matched cohort of COVID-19 patients without ILD.

AJRCCM 8/9/2020

Respiration

Editorial Comment

Respiration
DOI: 10.1159/000509523

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Published online: August 25, 2020

Management of Patients with Interstitial Lung Disease in the Midst of the COVID-19 Pandemic

Katerina M. Antoniou[a] Ganesh Raghu[b] Vasilios Tzilas[c] Demosthenes Bouros[c]

- Post-SARS fibrosis and IPF have distinct differences.
- Post-SARS fibrosis typically is not progressive, but nonetheless can be severe and limiting.
- The recovery period for post-SARS fibrosis is approximately one year and the residual deficits persist, but generally do not progress
- The available data so far are limited

Post COVID- 19 lung fibrosis

- Postmortem biopsies performed in Lille University
- 6 COVID-19 positive patients at different stages of the disease.
- 5 patients, who died the histologic pattern was an acute fibrinous and organizing pneumonia (AFOP), characterized by an extensive intra-alveolar fibrin deposition so-called fibrin «balls», rather than hyaline membranes.
- Need for International task force to provide a guidance on how to manage the new disease, COVID 19-ILD.

COVID-19 HISTOPATHOLOGICAL STAGES

DAD

ORGANIZING DAD

FIBROBLASTS

FIBROSIS@HC

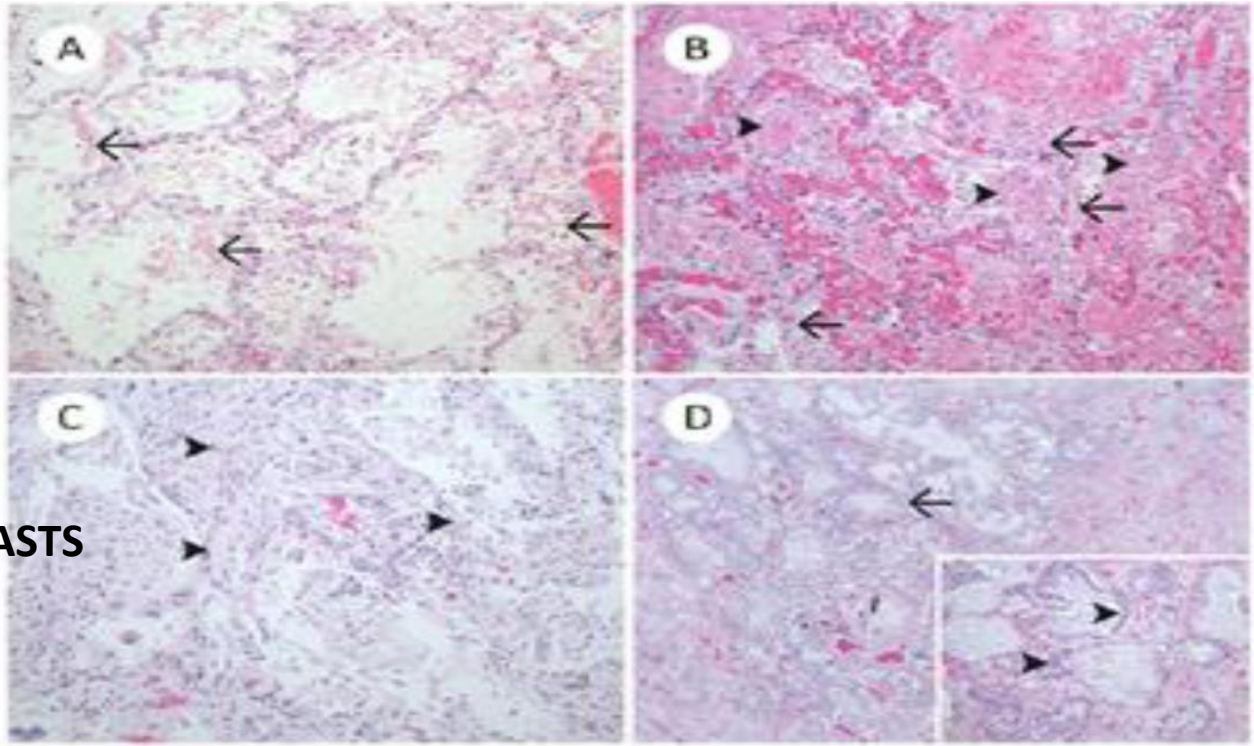


Figure 2 Histopathological findings demonstrating different stages of lung injury. (A) Acute diffuse alveolar damage (DAD) in the right upper lobe with hyaline membrane formation (←) (H&E ×100). (B) Organising DAD in the lower left lobe with haemorrhage, fibrin deposits (➤) and beginning organisation of immature fibroblasts (←) (H&E ×100). (C) Organisation of immature fibroblasts in the left upper lobe (➤). (D) Fibrosis with honeycomb-like remodelling in the right upper lobe (←) (H&E ×20) with bronchial metaplasia (➤) and marked chronic inflammation with primarily lymphocytes (H&E ×100).

IPF-COVID-19 Crucial questions

- One of the today's challenges for physicians treating ILDs patients is **how to protect and treat** them from COVID-19.
- **If they are mildly symptomatic or non-symptomatic can they return safely home or may deteriorate and will need hospitalization?**
- **Besides, it is important to differentiate the manifestation of superimposed COVID-19 from progression of their underlying fibrotic ILD and/or AE known.**

SARS-COV-2 PROPHYLAXIS

1. Travel restrictions, social distancing , self-quarantine, patient concerns, regulatory guidance, and sequestering of ILD staff have resulted in the majority of ILD outpatient visits being replaced by telephone consultation/video conferencing /Telemedicine, or rescheduled
2. Delay of elective procedures, including monitoring with PFTs, HRCTs and walk tests

SARS-COV-2 EFFECTS ON IPF

3. Oral medications are being delivered to the patient's home, and biological samples are being collected and processed at a local facility.
4. Patients are deprived of pulmonary rehabilitation.
5. The MDD are being done virtually, and treatment decisions are being made with suboptimal objective assessment over telephone.

Covid-19 and pulmonary fibrosis

- Approximately 30% of survivors of SARS and MERS experienced persistent radiological and physiological abnormalities consistent with fibrotic lung disease.
- Long-term follow-up studies will be required to establish the true prevalence of post-COVID-19 fibrosis.
- Role of anti-IL-1, anti- IL-6 *(nintedanib, pirfenidone)?*
- Well designed studies of antifibrotic therapies!

OVID-19 lockdown in Patients with ILD

Collateral benefits!

Early COVID-19 Lockdown in Greece and IPF:

A beneficial "impact" beyond any expectation

S.. Papiris[1], D. Bouros[2,3], K. Markopoulou[4], L. Kolilekas[5] et al.

Eur Respr Journal (submitted)

Retrospective study

1. *to assess the frequency,*
2. *characteristics and*
3. *outcome of COVID-19 disease in IPF patients*

in 11 specialized referral centers and 2 dedicated private practices all over Greece.

SARS-CoV-2 OVERVIEW

- **Study period from February 26th, 2020, *[when the first case of COVID-19 was confirmed in Greece]* to May 2020, *[where after a strict lockdown gradually lifted].***
- **Data concerning hospitalization of IPF patients of the Greek cohort and outcome were compared with data of the same time-period of the year 2019.**

SARS-CoV-2 OVERVIEW

550 IPF patients, median age 74 years, 80.7% male, 72% ever- smokers, and a median disease duration 26 months

458 (83.3%) were under pirfenidone or nintedanib

The majority suffered from at least one comorbidity: *diabetes mellitus (18.4%), arterial hypertension (51.3%), CHD (25.8%) and cancer (9.1%) and 6.1% on LTOT.*

Only 2 patients [one M 60 years-old and one F 91 years-old], recently diagnosed familial IPF developed COVID-19, both survived.

SARS-CoV-2 OVERVIEW

This study shows that during the strict COVID-19 lockdown applied in Greece, patients with IPF experienced much lower than expected COVID-19, since only a low number of IPF patients registered and followed-up regularly in specialized reference centers developed the disease.

At the same time a decrease in hospitalizations related to other LRTI and deaths of IPF patients were reported, compared to the corresponding three-month period of the year 2019.

SARS-CoV-2 -COPD

In a study performed in Hong Kong the number of admissions for COPD exacerbations decreased by 44% in first three months of 2020, compared with previous years due to the adoption of protective measures

Early COVID-19 Lockdown in Greece and IPF:

A beneficial "impact" beyond any expectation

S.. Papiris[1], D. Bouros[2,3], K. Markopoulou[4], L. Kolilekas[5] et al.

Eur Respr Journal (submitted)

LESSONS FROM THE PANDEMIC

During the lockdown, IPF patients experienced lower than expected COVID-19 suggesting that simple measures for the winter months, such as face masking, clean hands, physical distancing could be adopted as promising advances in non-pharmacological therapy.

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

Peter M George, Athol U Wells, R Gisli Jenkins

www.thelancet.com/respiratory Vol 8 August 2020

Given the scale of the pandemic, the global burden of fibrotic lung disease will probably increase considerably.

- **There is therapeutic rationale for the use of antifibrotic therapy in AE/IPF, including those triggered by viral infection.**
- **Available antifibrotic therapies have broad antifibrotic activity regardless of etiology, and might have a role in attenuating profibrotic pathways in SARS-CoV-2 infection.**

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

Peter M George, Athol U Wells, R Gisli Jenkins

www.thelancet.com/respiratory Vol 8 August 2020

Novel antifibrotic strategies have a range of antiviral and epithelial protective effects in models of acute and viral induced lung injury.

- **Close follow-up of patients after COVID-19 is essential.**
- **There is an urgent need for therapies that diminish severe**

COVID-19 and clinical trials of antifibrotic molecules should be considered.

	Inhibits viral infection or disease	Inhibits experimental acute lung injury	Inhibits IL-1 or IL-1 effects	Inhibits IL-6
Nintedanib	Not described	Not described	Yes[38,39]	Yes[40,41]
Pirfenidone	Not described	Yes[42]	Yes[43,44]	Yes[42]
αvβ6 integrin blockers and knockout mice	Yes[45,46]	Yes[47,48]	Yes[48]	Yes[49]
Gal-3 inhibitor and knockout mice	Yes[50,51]	Yes[51,52]	Yes[51]	Not described
Autotaxin inhibitor	Not described	Not described	Not described	Yes (skin);[53] not described
Lysophosphatidic acid inhibitor (BMS-986020; SAR100842)	No	Yes[54]	Not described	Yes (skin)[53]
JNK inhibitor	Yes[55-58]	Yes[59]	Not described	Yes
mTOR pathway modulator	Yes[60]	Yes[61]	Yes[61]	Yes[43]
SAP (also known as PTX2)	Yes[60,62,63]	Yes[64]	Not described	Not described
AT2R inhibitor	Not described	Yes[65,66]	No[44]	Yes[65]

Table: Potential link between antiviral mechanisms and antifibrotic drugs

SOCIÉTÉ CANADIENNE DE THORACOLOGIE

CANADIAN THORACIC SOCIETY

Optimizing care for patients with interstitial lung disease during the COVID-19 pandemic

Diagnostic evaluation of patients with ILD

We suggest modifying the standard diagnostic evaluation to reduce in-person patient contact with the healthcare system in order to minimize the risk of SARS-CoV-2 transmission.

Ancillary diagnostic procedures including bronchoscopy and surgical lung biopsy

Beyond usual risk-benefit considerations, additional risk factors associated with the transmission of SARS-CoV-2 and development of severe COVID-19 illness should be considered when contemplating aerosol generating medical procedures such as bronchoscopy and surgical lung biopsy.

SOCIÉTÉ CANADIENNE DE THORACOLOGIE

CANADIAN THORACIC SOCIETY

Optimizing care for patients with interstitial lung disease during the COVID-19 pandemic

Antifibrotic medications

We suggest that antifibrotic therapies should continue to be prescribed according to clinical practice guideline recommendations.

Patient care after COVID-19 disease

We suggest that patients with persistent respiratory symptoms after COVID-19 illness be evaluated for the presence of post-COVID pulmonary fibrosis and/or exacerbation of pre-existing ILD, and that patients with confirmed post-COVID pulmonary fibrosis be assessed at a clinic that specializes in ILD.

Suggested approach to the care of patients with ILD in the midst of the COVID-19 pandemic.

Guidelines to decrease risks of exposure *(social distancing, masks , isolation, self-quarantine, appropriate testing for COVID -19 , etc)*
Postpone elective follow ups and laboratory examinations, if stable
IPF patients on antifibrotic: continue treatment
Telemedicine , phone visits , virtual medicine
Prompt evaluation for suspected COVID-19
If hospitalized for COVID-19, antifibrotics may be held until patient stabilizes
ILD patients on immunomodulating /immunosuppressive agents, including corticosteroids): seek prompt medical attention for respiratory symptoms; reduce dosage or stop medications (case by case basis) and monitor closely
Newly diagnosed patients with IPF: no need to hold antifibrotics.

CANADIAN THORACIC SOCIETY
ICU TRIAGE FOR PULMONARY FIBROSIS PATIENTS
SUMMARY OF RECOMMENDATIONS

Level 1 (>80% predicted mortality during critical illness or in the 6-12 months following critical illness)

PULMONARY FIBROSIS

FVC <50-60%; **OR**

DLCO <30-40% predicted; **OR**

Chronic supplemental oxygen at home (more than 12 hours per day); **OR**

Echocardiographic evidence of pulmonary hypertension (estimated right ventricular systolic pressure >50 mmHg)[a]; **OR**

Rapidly progressive disease[b]; **OR**

History of Acute Exacerbation-Interstitial Lung Disease in the last 12 months.

CANADIAN THORACIC SOCIETY
ICU TRIAGE FOR PULMONARY FIBROSIS PATIENTS
SUMMARY OF RECOMMENDATIONS

Level 2 (>50% predicted mortality during in the 6-12 months following critical illness).

PULMONARY FIBROSIS

FVC <50-60% **OR**

DLCO <30-40% predicted; **OR**

Chronic supplemental oxygen at home (more than 12 hours per day); **OR**

Echocardiographic evidence of pulmonary hypertension (estimated right ventricular systolic pressure >50 mmHg)[a]; **OR**

Rapidly progressive disease[b] **OR**

History of Acute Exacerbation-Interstitial Lung Disease in the last 12 months. (**Same as Level 1**)

CANADIAN THORACIC SOCIETY
ICU TRIAGE FOR PULMONARY FIBROSIS PATIENTS
SUMMARY OF RECOMMENDATIONS

Level 3 (>30% predicted mortality during or in the 6-12 months following critical illness).

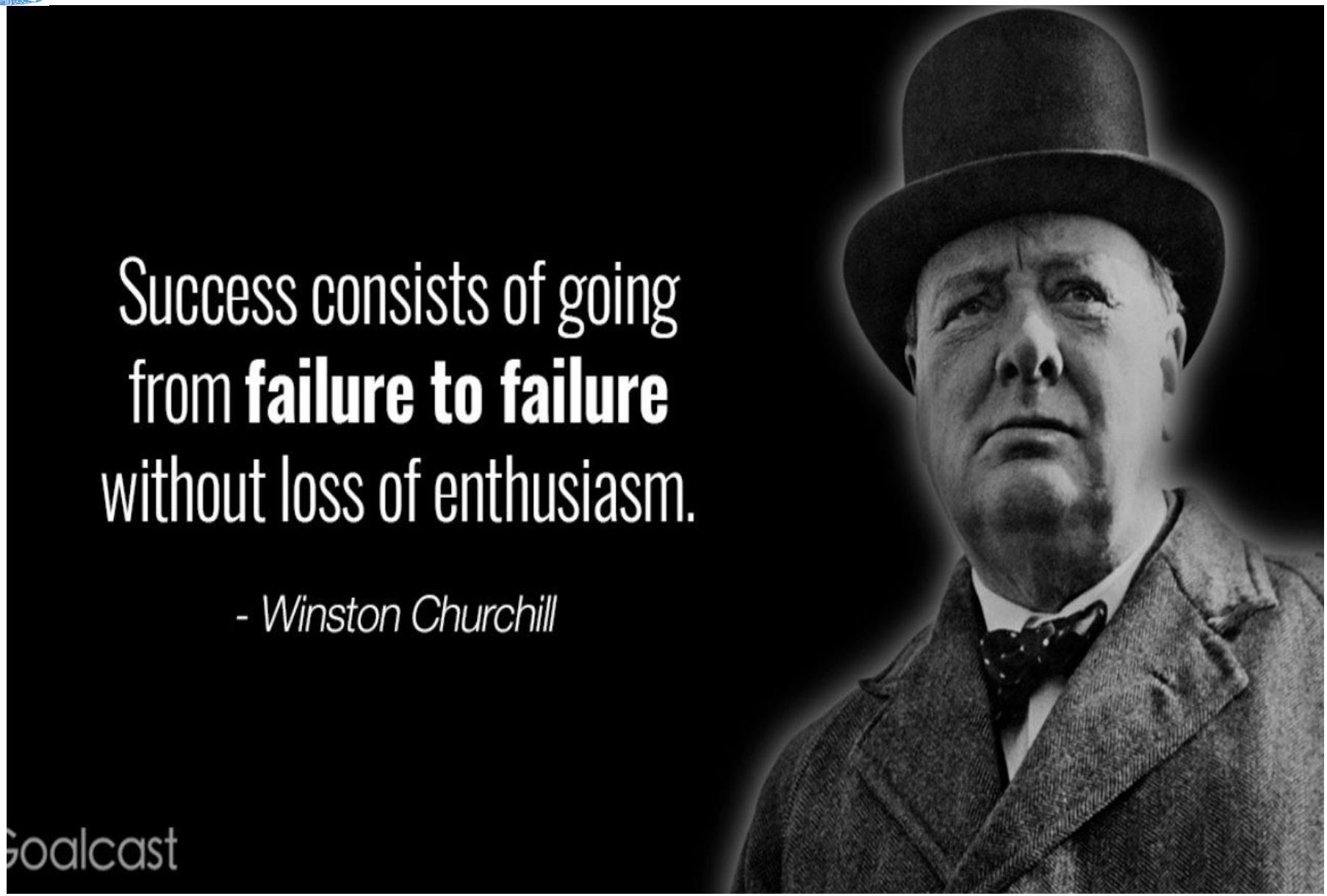
PULMONARY FIBROSIS

FVC <75%; **OR**

DLCO <55% predicted.

Additional factors to consider at all surge levels

Lung cancer

CHD/CAD

THE COVID-19 STORY