

Interstitial Lung Disease in the COVID-19

Era

2021-04-10

건국대학교 병원 호흡기내과 김희정



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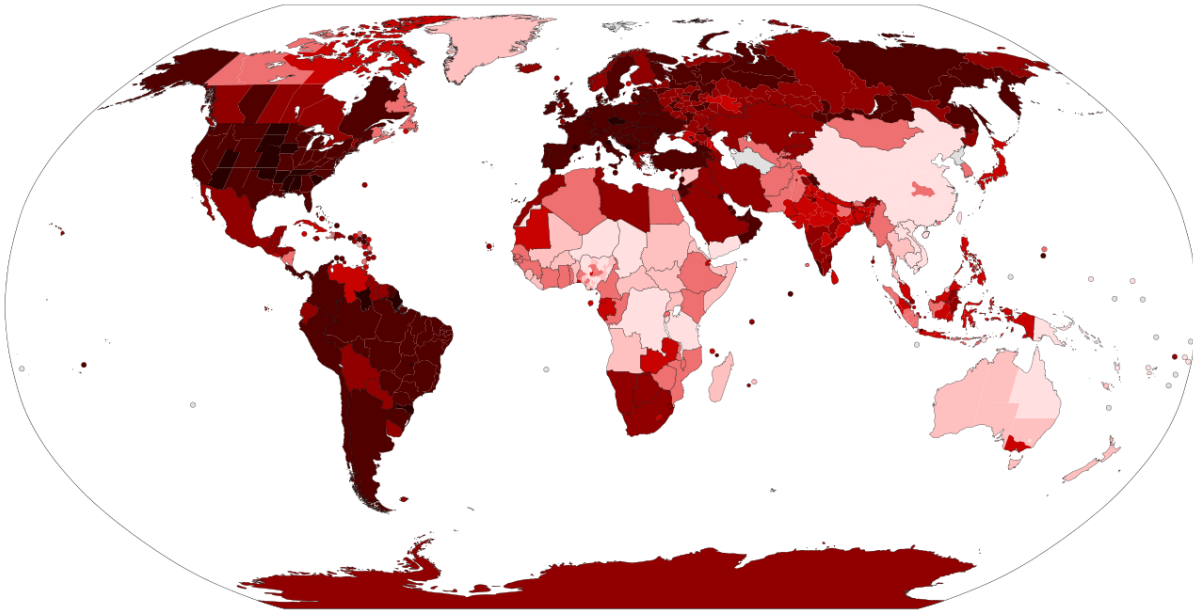
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Introduction



COVID-19 pandemic 



Healthcare systems 

- Primary care and specialist physicians
- Investigations, procedures, and elective surgeries
- Critical resources; ventilators

Introduction

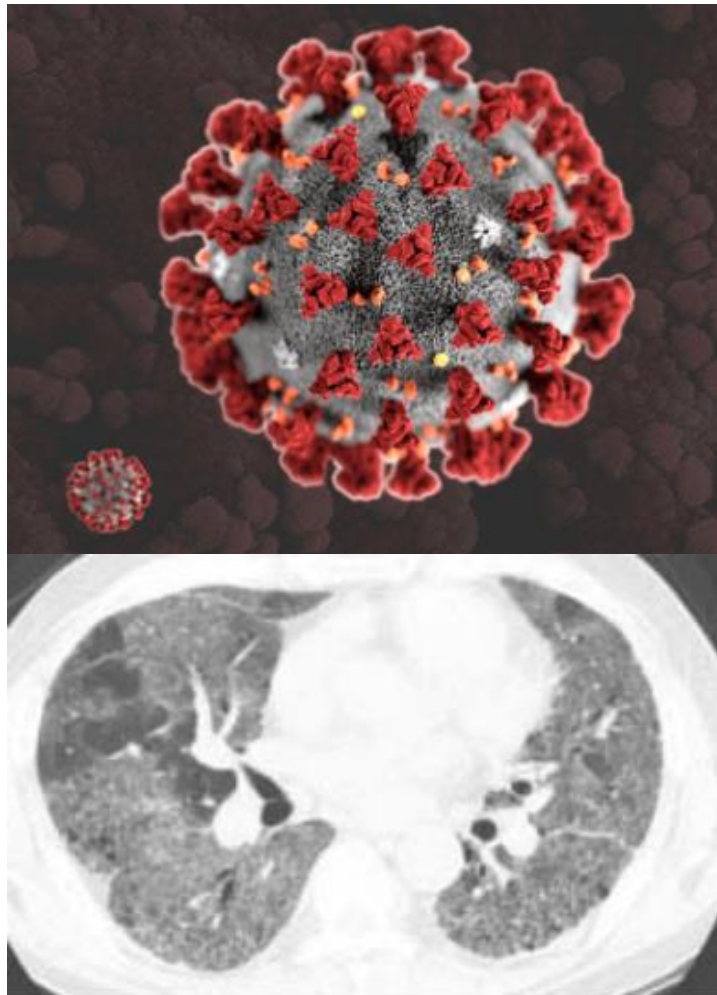


Table 1. Clinical Characteristics of Patients with COVID-19 and Comorbid ILD Compared with a Matched Cohort of Patients with COVID-19 without Comorbid ILD

	ILD (n = 46)	No ILD (n = 92)	Odds Ratio (95% CI)	P Value
Patient characteristics				
Age, yr, median (IQR)	69 (58–78)	69 (59–78)	NA	NS
Sex, M, n (%)	16 (35)	32 (35)	NA	NS
Race, n (%)				
White	19 (41)	38 (41)	NA	NS
Black	9 (20)	27 (29)	NA	
Hispanic	12 (26)	13 (14)	NA	
Other	6 (13)	14 (15)	NA	
BMI, kg/m ² , median (IQR)	27.6 (22.5–33.2)	28.7 (23.7–33.5)	NA	NS
Smoking status, n (%)				
Never-smoker	19 (41)	57 (62)	NA	0.07
Current smoker	4 (9)	5 (5)	NA	
Former smoker	23 (50)	30 (33)	NA	
Pack-years, median (IQR)	32.5 (15.0–40.0)	15.0 (8.0–27.8)	NA	NS
Comorbidities, n (%)				
Diabetes mellitus	16 (35)	31 (34)	NA	NS
Hypertension	35 (76)	62 (67)	NA	NS
Cardiovascular disease	23 (50)	30 (33)	NA	0.06
Obstructive lung disease	15 (33)	25 (27)	NA	NS
Chronic therapies, n (%)				
Home oxygen supplementation	5 (11)	3 (3)	NA	NS
Inhaled corticosteroid	10 (22)	15 (16)	NA	NS
Long-acting β -agonist	7 (15)	6 (7)	NA	NS
Long-acting muscarinic antagonist	3 (7)	1 (1)	NA	NS
Corticosteroid	11 (24)	4 (4)	NA	0.001
Other immunosuppression*	18 (39)	7 (8)	NA	<0.001
ACEi/ARB	17 (37)	32 (35)	NA	NS
Nonsteroidal antiinflammatory	7 (15)	8 (9)	NA	NS
Outcomes, n (%)				
Hospital admission[†]				
Hospital admission [†]	34 (74)	53 (58)	2.1 (0.9–4.6)	0.07
ICU level of care	16 (47)	12 (23)	3.0 (1.2–7.9)	0.02
Mechanical ventilation	13 (81)	11 (92)	0.4 (0.03–3.1)	NS
Length of stay, d	7 (5–13)	7 (5–14)	NA	NS
Discharged				
Discharged	17 (50)	45 (85)	0.2 (0.06–0.5)	<0.001
Home	9 (28)	31 (58)	0.3 (0.1–0.7)	0.008
Skilled nursing facility	8 (25)	14 (26)	0.9 (0.3–2.6)	NS
Death	15 (33)	12 (13)	3.2 (1.3–7.3)	0.01

Viral infection ➡ Acute exacerbation of ILD ➡ Poor prognosis

Esposito AJ, et al. *Am J Respir Crit Care Med.* 2020;202(12):1710-1713.

Impacts of COVID-19 in patients with ILD

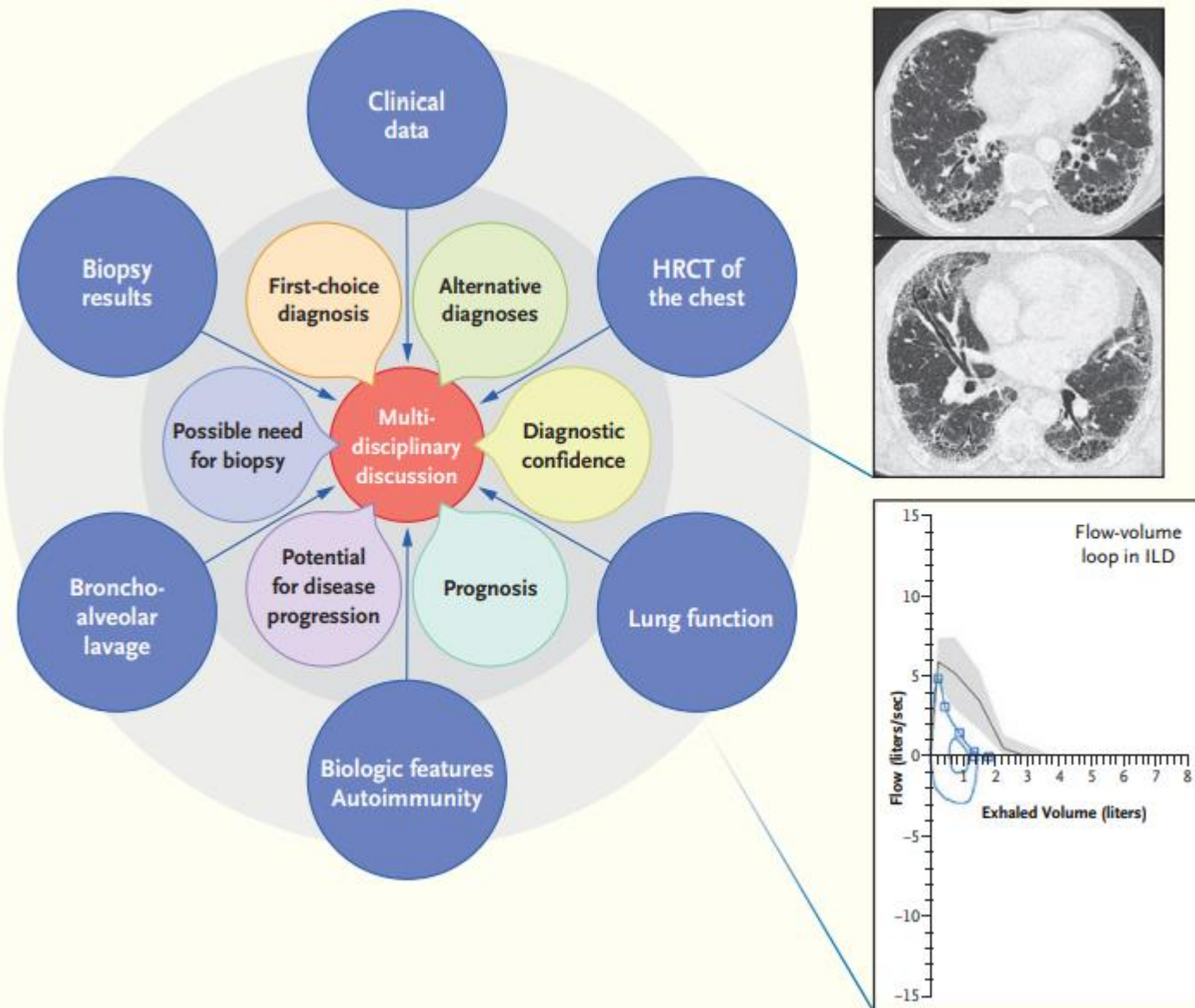
Rapidly evolving situation ; Mutant strains, Strategies of social distancing
Limited evidence to guide specific recommendations

▶ Aspects of patient care

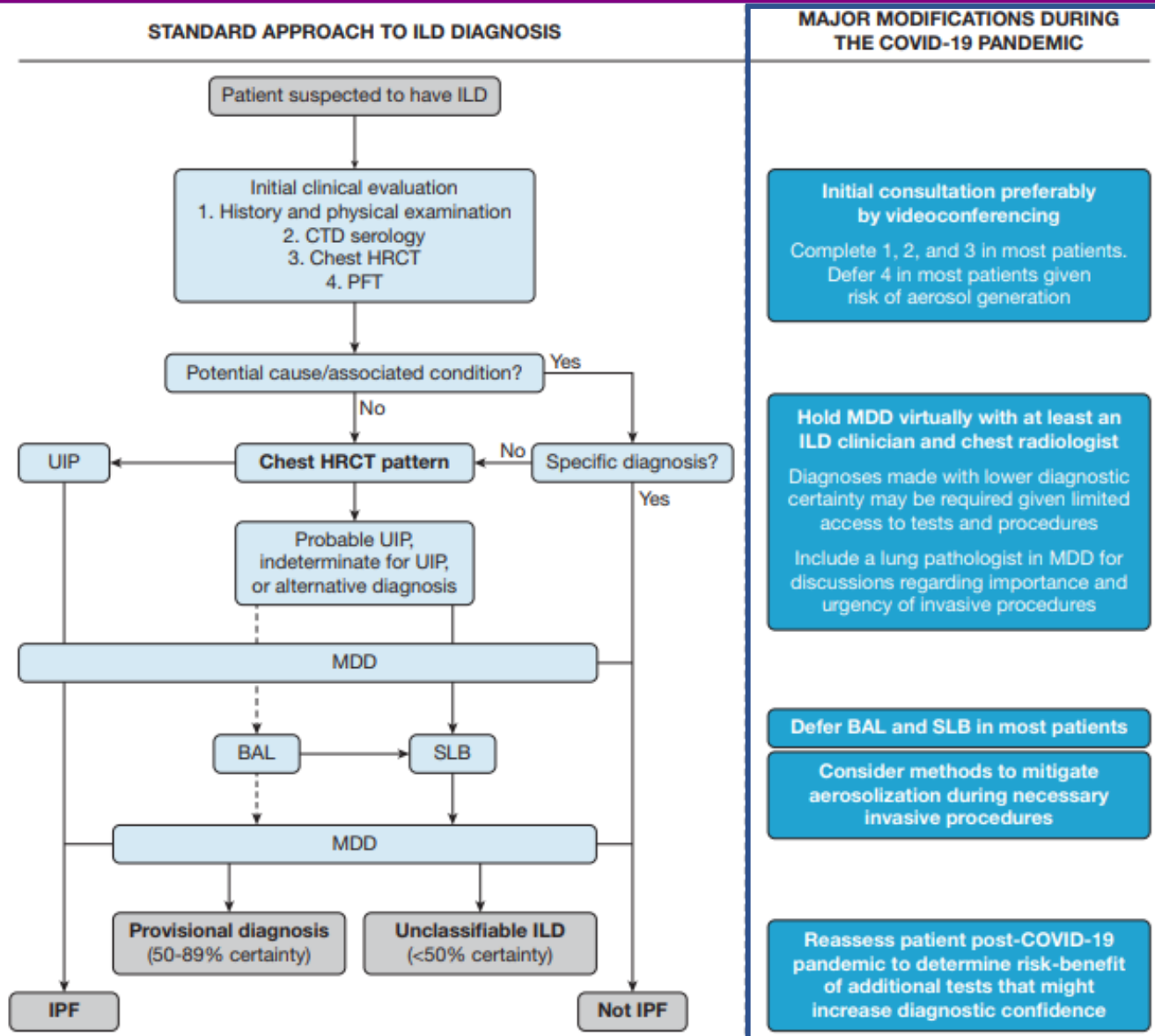
- Diagnostic process
- Initiation, maintenance, and monitoring of ILD therapy

▶ Research activities

Diagnosis of ILD



Initial ILD assessment



- ▶ Minimizing delays in diagnosis and management
- ▶ Avoiding nonessential contact with the health-care system
 - History and physical exam
 - Blood work; autoimmune serology
 - Imaging study; HRCT
 - **PFT**; higher risk of spreading infection
 - Essential components (spirometry or DLCO) in patients suspected of ILD
 - Postponing a presurgical PFT/ Routine PFTs for patients with symptomatically stable disease

More invasive tests

► Bronchoscopy; Bronchoalveolar lavage, Transbronchial lung cryobiopsy

TABLE 1 Bronchoalveolar lavage (BAL) findings that are useful in interstitial lung disease diagnosis

BAL finding	Consistent interpretation/suggested diagnosis
Eosinophils $\geq 25\%$	Eosinophilic pneumonia
Lymphocytes $\geq 25\%$	Sarcoidosis, HP, cellular NSIP, drug reaction, CBD, LIP, lymphoproliferative disorder
Neutrophils $\geq 50\%$	AIP, DAD, AEIPF, pulmonary infection
Bloody fluid	Pulmonary haemorrhage, DAH
High haemosiderin score	DAH, DAD
CD1a+ cells $>4\%$	PLCH
Milky BAL fluid with PAS-positive amorphous debris	PAP
Monotypic lymphocytes	Pulmonary lymphomatous malignancy
Malignant cells	Pulmonary malignancy
Squamous epithelial cells $>5\%$	Unsuitable sample due to upper airway secretion contamination
Bronchial epithelial cells $>5\%$	BAL sample may be unsuitable for cell analysis

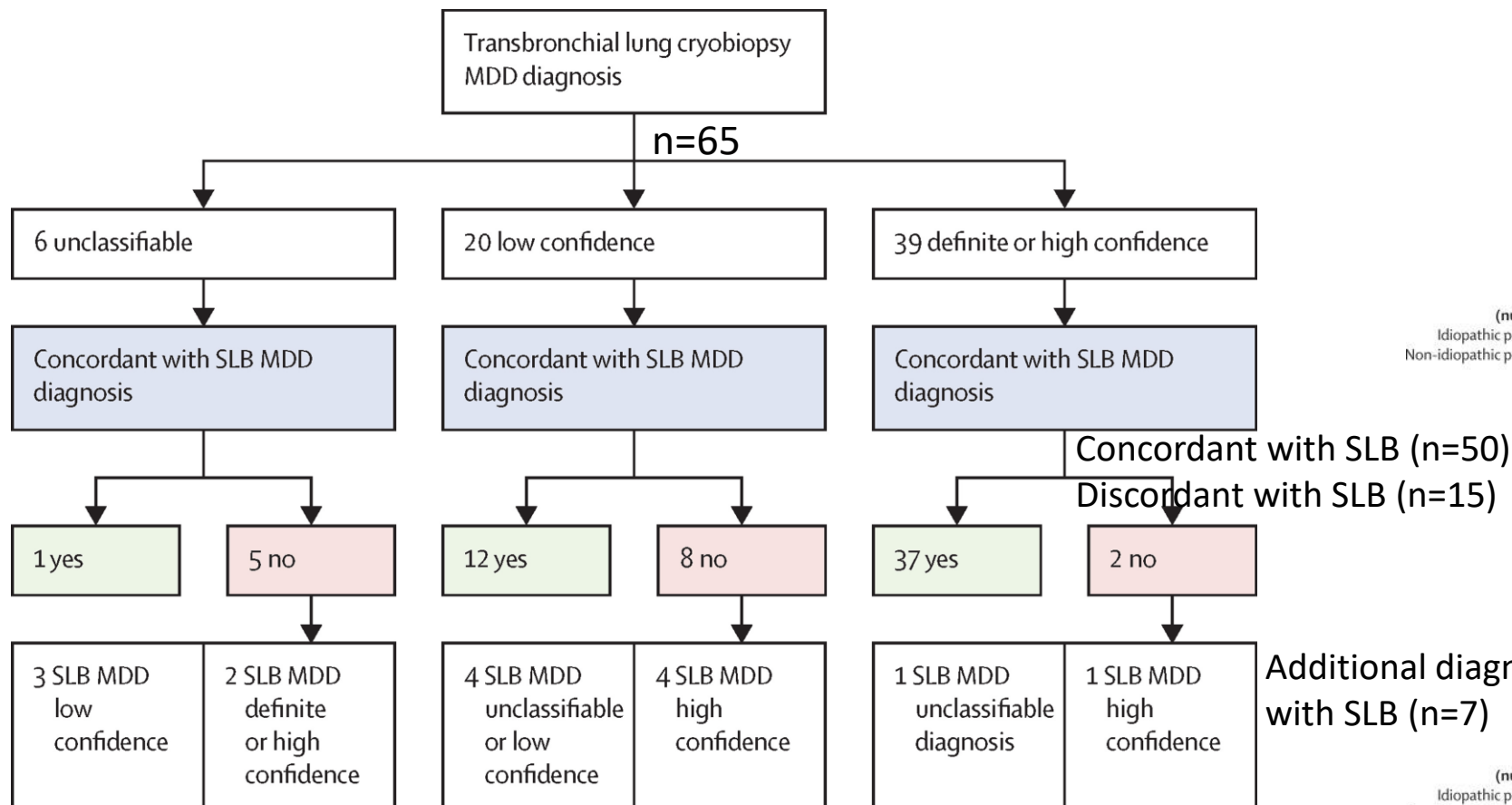
PAS: periodic acid–Schiff staining; HP: hypersensitivity pneumonitis; NSIP: nonspecific interstitial pneumonia; CBD: chronic beryllium disease; LIP: lymphoid interstitial pneumonia; AIP: acute interstitial pneumonia; DAD: diffuse alveolar damage; AEIPF: acute exacerbation of interstitial pulmonary fibrosis; DAH: diffuse alveolar haemorrhage; PLCH: pulmonary Langerhans cell histiocytosis; PAP: pulmonary alveolar proteinosis.

More invasive tests

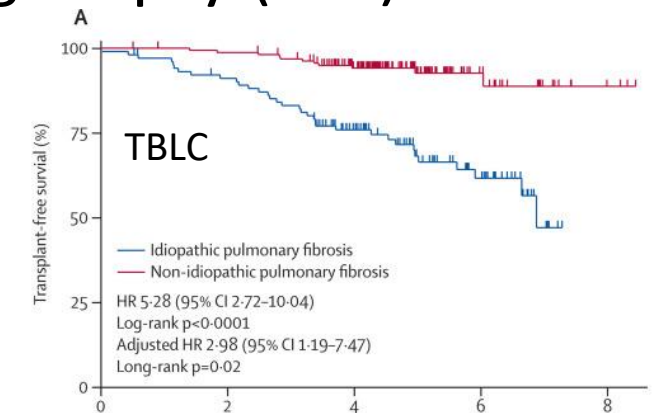
► Transbronchial lung cryobiopsy (TBLC)/ Surgical lung biopsy (SLB)

- Diagnostic accuracy

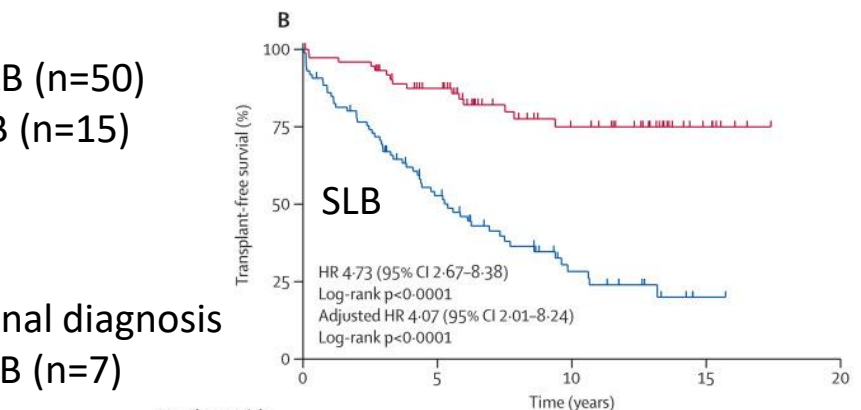
- Prognosis



Troy LK et al. *Lancet RM* 2020; 8(2):171-181.



	Number at risk (number censored)				
	0	2	4	6	8
Idiopathic pulmonary fibrosis	103 (0)	91 (3)	61 (16)	23 (30)	0 (20)
Non-idiopathic pulmonary fibrosis	163 (0)	158 (3)	122 (29)	25 (96)	3 (22)



	Number at risk (number censored)				
	0	5	10	15	20
Idiopathic pulmonary fibrosis	86 (0)	40 (7)	13 (11)	1 (10)	0 (1)
Non-idiopathic pulmonary fibrosis	74 (0)	56 (4)	28 (23)	7 (21)	0 (7)

Tomassetti S, et al. *Lancet RM* 2020; 8(8):786-794.

Decisions to perform more invasive tests

► Bronchoscopy and/ or Surgical lung biopsy (SLB)

Potential diagnostic usefulness  Possible complications + Pandemic

Postpone

- If a patient already has a confident diagnosis (> 90% certainty), then further testing is unlikely to alter management decisions
- > 75 years old (younger age threshold is needed)

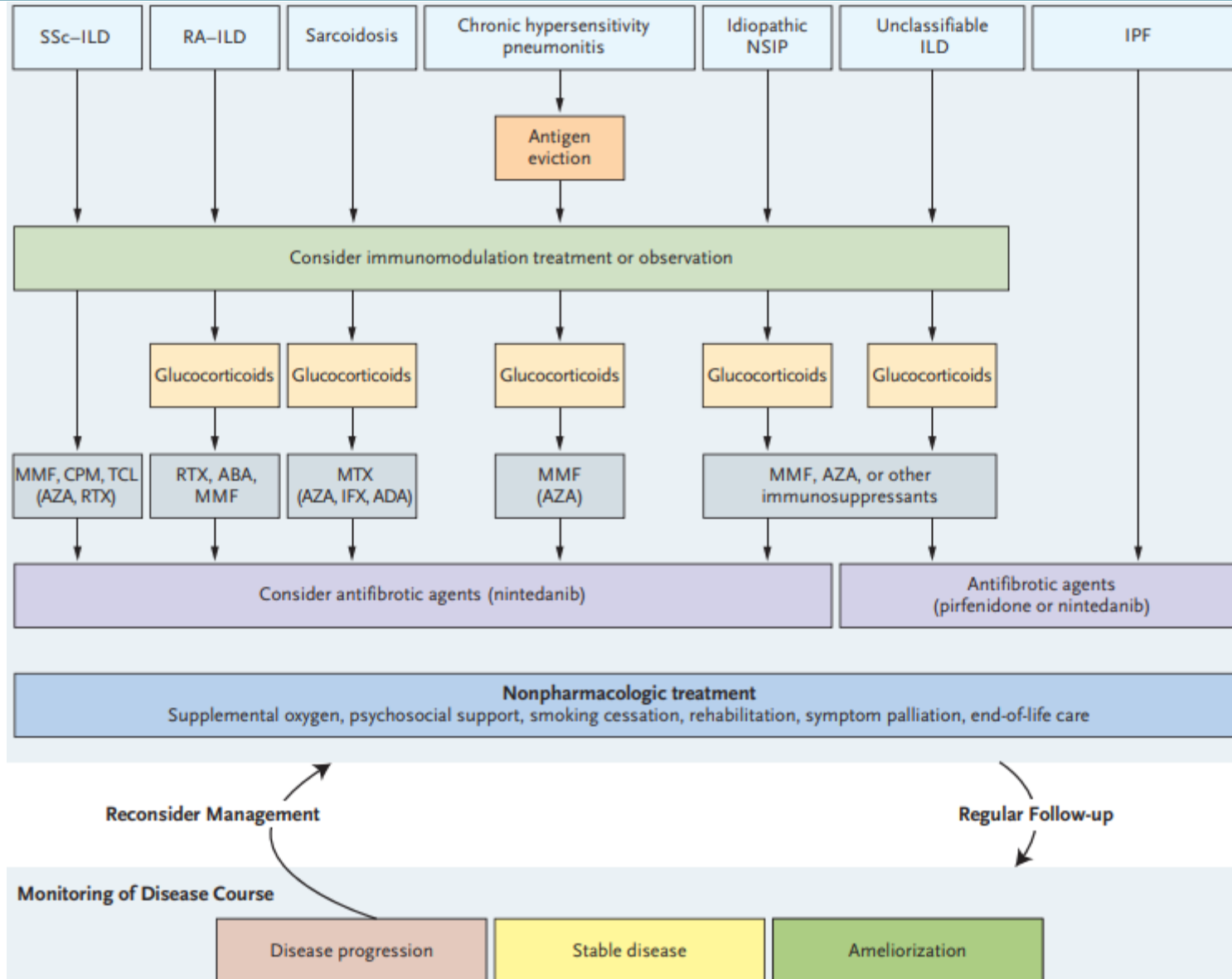
Different strategies

- Provisional diagnosis (50%-89% vs. < 50% certainty)
- Context of the COVID-19 pandemic
 1. Observed if stable
 2. Empirically treated
 3. More invasive diagnostic procedures

Perform

- Based on a virtual multidisciplinary discussion (MDD)
- Whether the result of this test is expected to impact short-term management decisions
- COVID-19 testing before procedure

Treatment

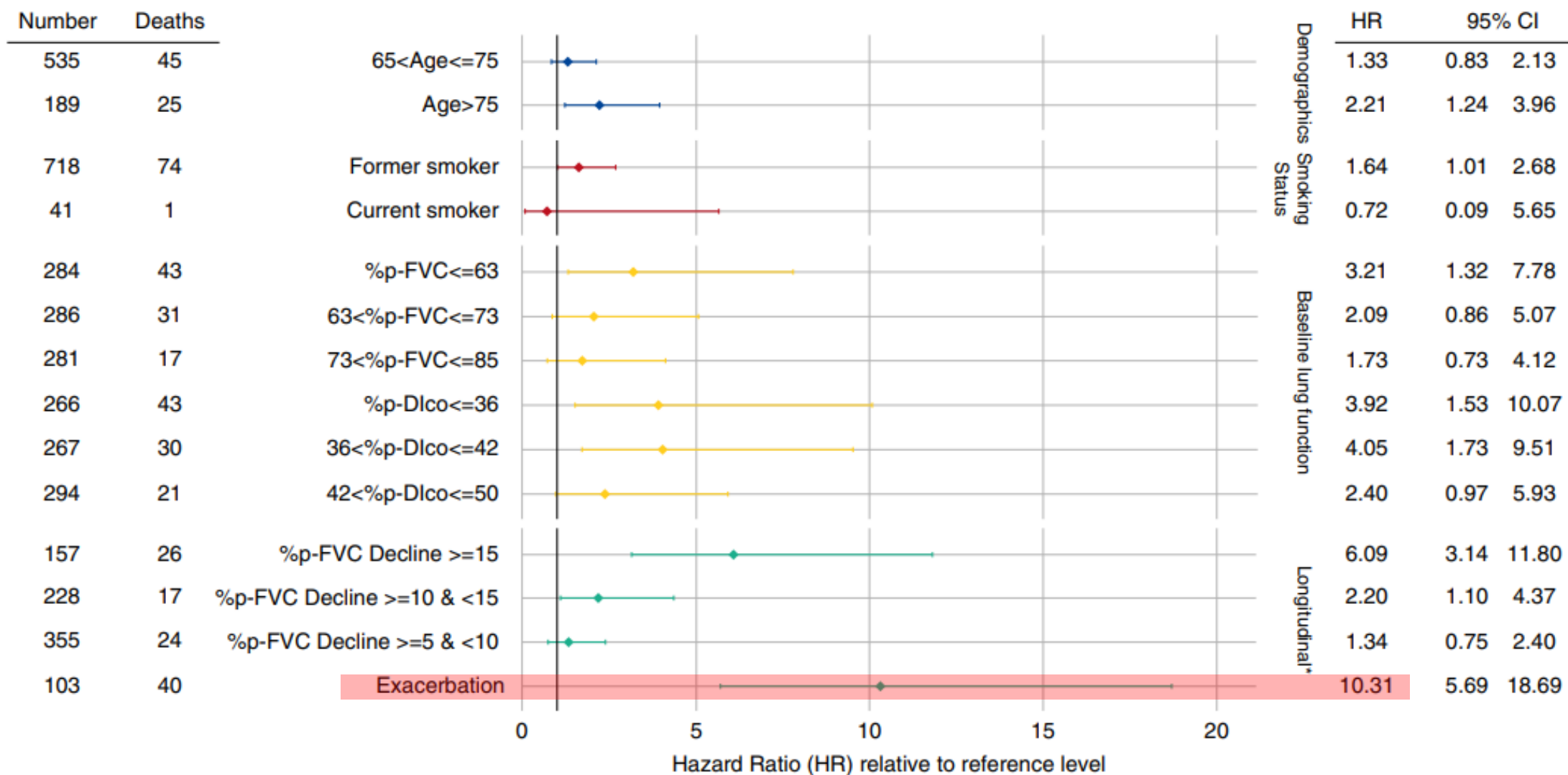


- ▶ Risk stratification
- ▶ Treatment of ILD
- ▶ Mixture of two diseases; ILD and COVID-19
- ▶ Monitoring

Risk stratification of ILD

Condition	Age	Sex	Race	Severity	Comorbidities	Others
IPF	older	Male		Honeycombing or UIP pattern on CT, FVC < 70%		
SSc-ILD		Male	Black	Diffuse cutaneous SSc, disease extent on CT > 20%, reduced FVC and DLco		< 7yr since diagnosis, anti Scl-70 Abs
RA-ILD	older	Male		disease extent on CT > 20%, Honeycombing or UIP pattern on CT, FVC < 70%		
Sarcoidosis, fibrotic		Female	Black	Disease extent on CT > 20%	Pulmonary hypertension	
Chronic fibrotic HP				Honeycombing or UIP pattern on CT		Persistent exposure to offending Ag
Unclassifiable fibrotic ILD				Honeycombing on imaging, progressive decline in lung function		

Risk factors for mortality in IPF



Treatment; Immunomodulatory medications

- ▶ Prednisone, MMF, azathioprine, cyclophosphamide, rituximab
- ▶ Corticosteroids may be harmful in early stages of infection
- ▶ Immunosuppressed patients similarly do not appear to have an increased risk for or severity of COVID-19

- ▶ Initiation of immunomodulatory therapy
 - Reasonable to use in most patients with progressive disease
 - Preferably limiting the use of corticosteroids and prioritizing steroid-sparing therapies
 - Delay initiation of nonurgent therapy if there is limited likelihood of shortterm progression

- ▶ Maintenance of immunomodulatory therapy
 - At least low doses of immunomodulatory therapy
 - Prioritizing steroid-sparing medications over prednisone

Treatment; Antifibrotic medications

▶ Nintedanib, Pirfenidone

- No evidence that antifibrotic therapies impact the risk or severity of COVID-19
- Overlap between adverse effects of these medications and symptoms of COVID-19 (eg, diarrhea, fatigue, loss of appetite)
- Difficulty in obtaining PFTs and conducting MDDs in places with a high burden of COVID-19 → limit fulfillment of criteria for prescribe
- Consistent benefits of antifibrotic therapy across severities of IPF and in patients with non-IPF fibrotic ILD

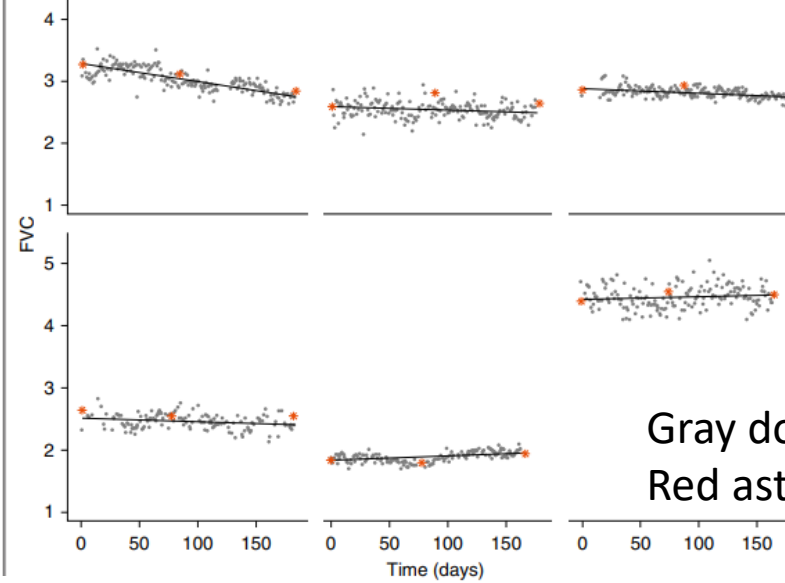
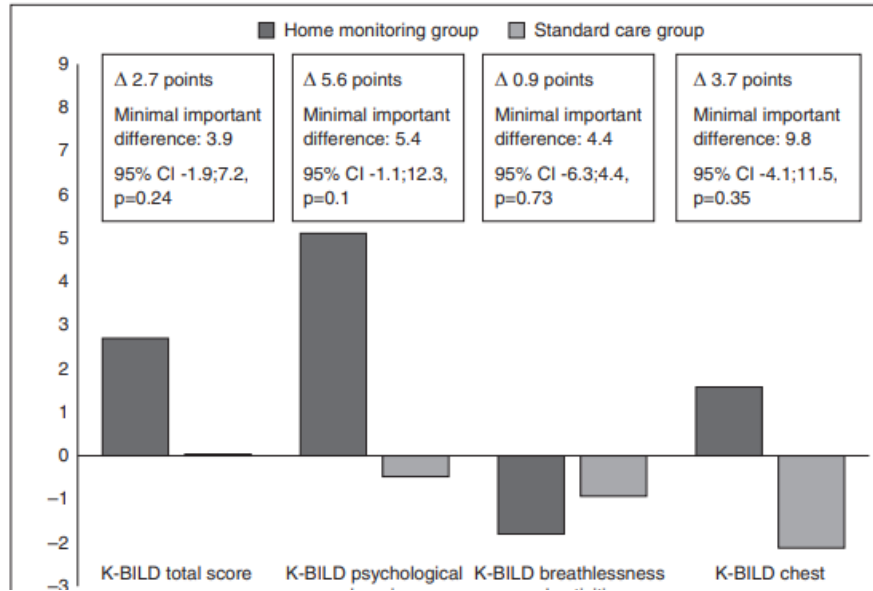
Nonpharmacologic Therapies and Supports

- ▶ Physical (social) distancing
- ▶ Exercise
- ▶ Smoking cessation
- ▶ Home oxygen
- ▶ Encouraged to maintain social support through virtual means (eg, online patient support groups or phone/video calls with friends and family)
- ▶ Lung transplantation
 - Need critical health-care resources : operating room time, critical care beds, personal protective equipment, health-care worker time
 - Many programs are choosing to postpone all but the most urgent cases

Monitoring of pharmacologic therapies

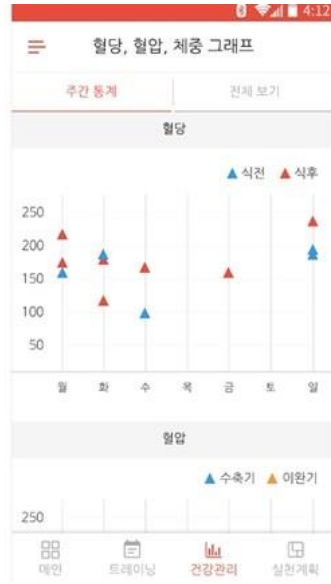
- ▶ **Bloodwork** monitoring for many ILD medications
 - Decrease monitoring frequency during the COVID-19 pandemic to minimize patient contact with the health-care system
 - In patients starting on ILD therapy, the potential for significant complications (eg, hepatotoxicity) will mandate blood-work monitoring on a regular basis over the short term
 - Lymphopenia
 - First finding during the acute phase of COVID-19 vs. AE of immunomodulatory therapy
- ▶ Routine **PFTs** for the purpose of ensuring ongoing medication coverage should be deferred in areas with a high burden of COVID-19
 - Symptomatic stability should instead be used as evidence of stability

Feasibility of Home monitoring



	Home Monitoring (n = 38)	Standard Care (n = 39)	Difference (95% CI)	P Value
Patients with extra hospital or GP visits, n (%)	13 (31.7)	10 (25.6)	—	0.55
Hospitalizations, n*	6	4	—	0.27
Change from baseline in HADS score at 24 wk				
Anxiety [†]	0.13 ± 0.35	0.18 ± 0.38	-0.05 (-1.08 to 0.99)	0.93
Depression [†]	0.34 ± 0.43	0.74 ± 0.43	-0.40 (-1.61 to 0.81)	0.51
Change from baseline in EQ-5D-5L score at 24 wk				
Index value [‡]	0.02 ± 0.02	-0.03 (0.17)	0.05 (-0.01 to 0.10)	0.11
VAS scale [‡]	-0.89 ± 3.6	-4.84 ± 2.8	3.95 (-5.20 to 13.10)	0.39
Change from baseline in GRC score at 24 wk [‡]	0.34 ± 0.35	-0.70 ± 0.40	1.03 (-0.02 to 2.09)	0.055
Change from baseline in VAS scores at 24 wk				
General well-being [‡]	0.65 ± 0.36	-0.39 ± 0.31	1.04 (0.09 to 2.00)	0.032
Cough [‡]	0.51 ± 0.45	-0.31 ± 0.50	0.82 (-0.52 to 2.17)	0.23
Dyspnea [‡]	0.41 ± 0.32	-0.23 ± 0.30	0.63 (-0.23 to 1.50)	0.15
Fatigue [‡]	0.46 ± 0.40	0.28 ± 0.35	0.18 (-0.88 to 1.23)	0.74
Stability IPF [‡]	0.49 ± 0.31	-0.6 ± 0.52	1.09 (-0.12 to 2.29)	0.076

Home monitoring in Korea



복합만성질환자
생체정보 모니터링

원격모니터링



공공시설및도서벽지 만성
질환자생체정보 모니터링

원격진료 및 처방



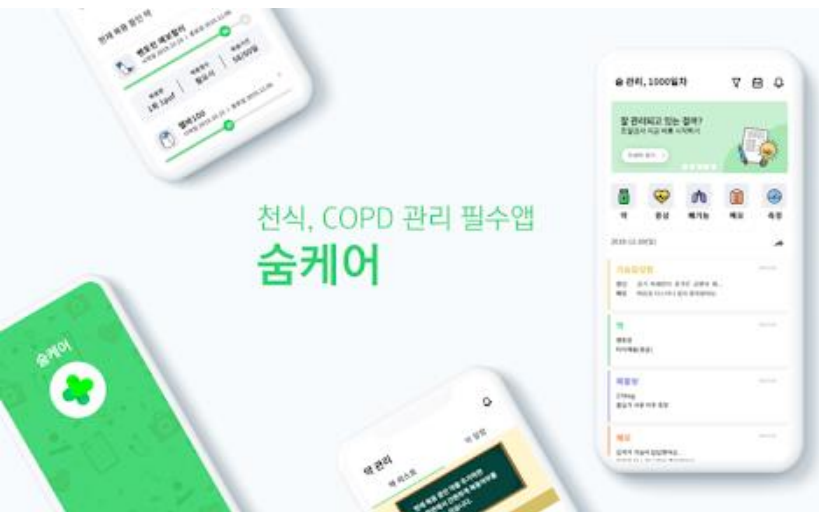
노인요양시설내 만성질환자
생체정보 모니터링

원격진료 및 처방



고혈압·당뇨환자
생체정보 모니터링

원격진료/원격모니터링



Home monitoring in Korea

2019년 경제정책방향

(1) 핵심규제 혁신

보건의료 서비스 확대

- 만성질환자 맞춤형 케어플랜 → 스마트폰 등 비대면 모니터링

환자의 건강·생활을 모니터링하여
맞춤형 교육·상담 등 서비스 제공



- 일차의료기관에서 만성질환자에 대한 맞춤형 케어플랜을 수립하고, 스마트폰 등을 활용한 비대면 모니터링* 사업 추진

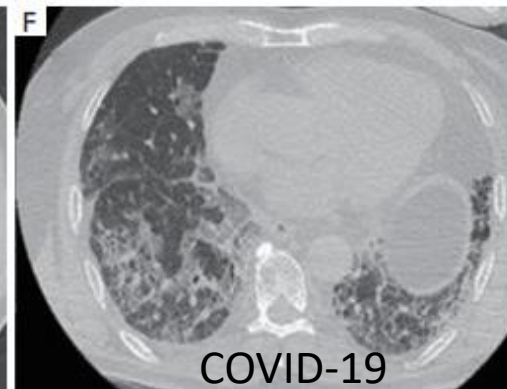
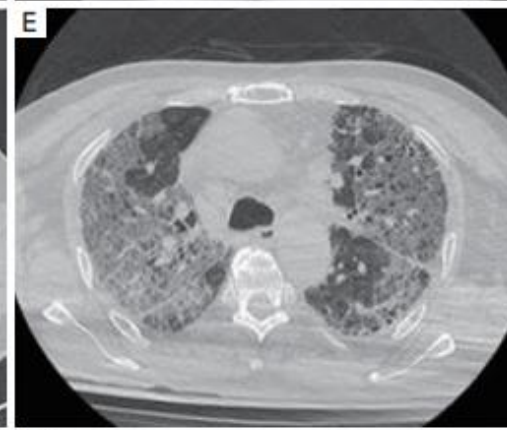
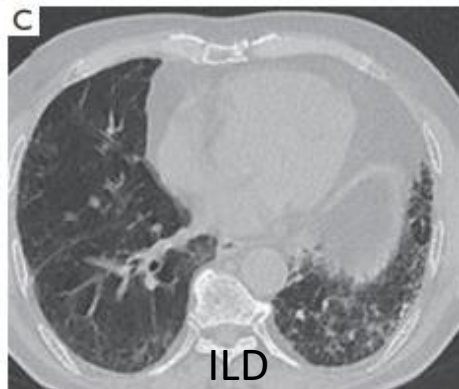
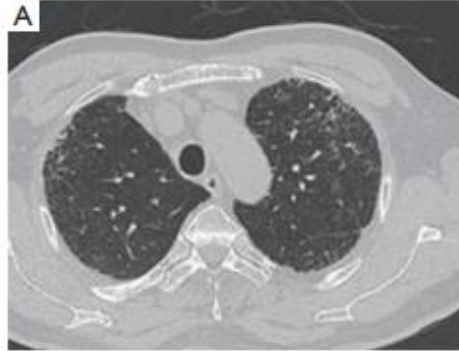
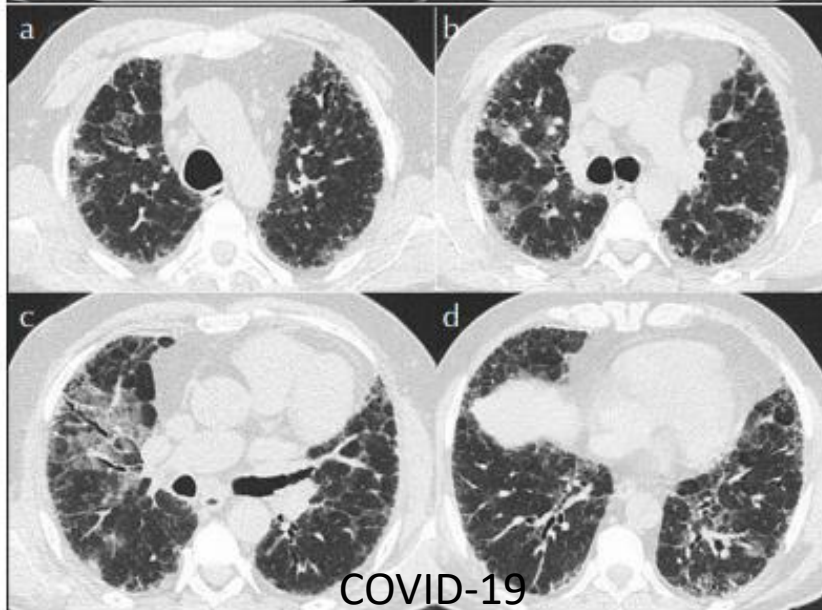
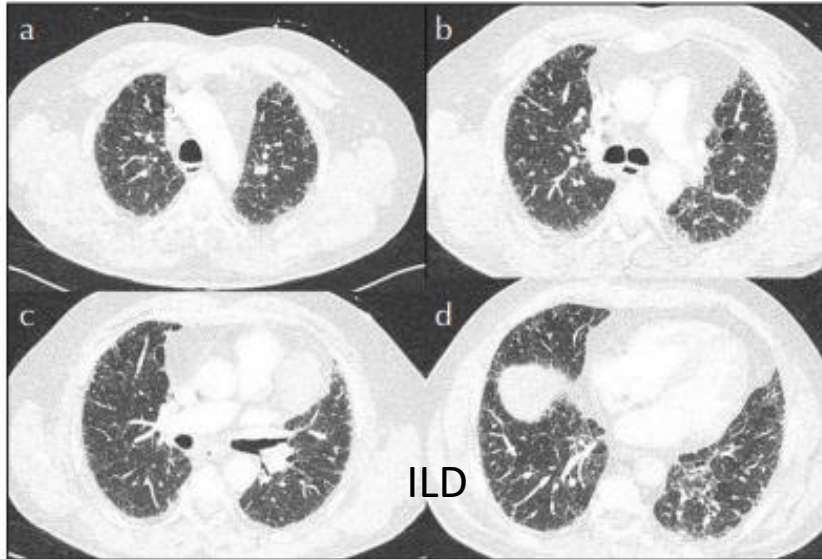
* 환자의 건강·생활을 모니터링하여 맞춤형 교육·상담 등 환자관리 서비스 제공

- 만성질환관리 시범사업 실시 및 수가체계 마련

- 非의료기관의 건강관리 서비스 제공범위·기준을 연내 마련하고, 실제 현장적용을 위한 적용사례집 발간('19.1/4)

* (現) 의료법상 의료행위-비의료행위 구분이 불명확하여 건강관리서비스 활성화 애로

COVID-19 in patients with ILD



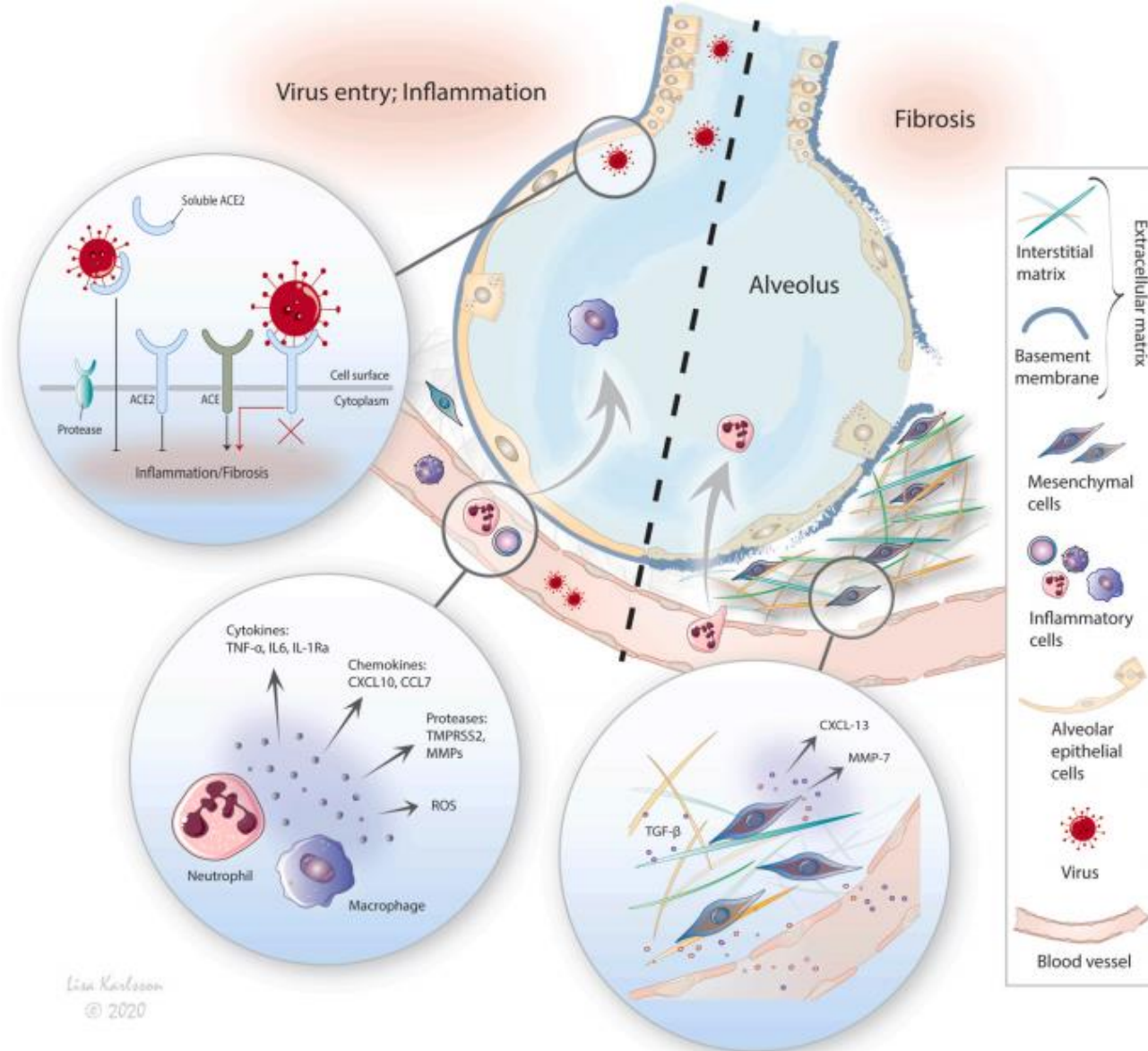
► Symptoms

- Mild (81%)
Fever, cough, dyspnea
- Severe (14%)
Respiratory distress, hypoxemia
- Respiratory failure (5%)

Uzel FI, et al. *Turk Thorac J*
2020; 21(6): 451-3.

Lee YH, et al. *J Thorac Dis*
2020;12(7):3902-3904.

Pathogenesis of SARS-CoV-2



► Immunomodulatory and antifibrotic medications

Diagnosis of COVID-19

Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Specimens and values	Bronchoalveolar lavage fluid (n = 15)	Fibrobronchoscope brush biopsy (n = 13)	Sputum (n = 104)	Nasal swabs (n = 8)	Pharyngeal swabs (n = 398)	Feces (n = 153)	Blood (n = 307)	Urine (n = 72)
Positive test result, No. (%)	14 (93)	6 (46)	75 (72)	5 (63)	126 (32)	44 (29)	3 (1)	0
Cycle threshold, mean (SD)	31.1 (3.0)	33.8 (3.9)	31.1 (5.2)	24.3 (8.6)	32.1 (4.2)	31.4 (5.1)	34.6 (0.7)	ND
Range	26.4-36.2	26.9-36.8	18.4-38.8	16.9-38.4	20.8-38.6	22.3-38.4	34.1-35.4	
95% CI	28.9-33.2	29.8-37.9	29.3-33.0	13.7-35.0	31.2-33.1	29.4-33.5	0.0-36.4	

Table 2. Performance of the RT-PCR test and CT scan in diagnosing SARS-CoV2 infection

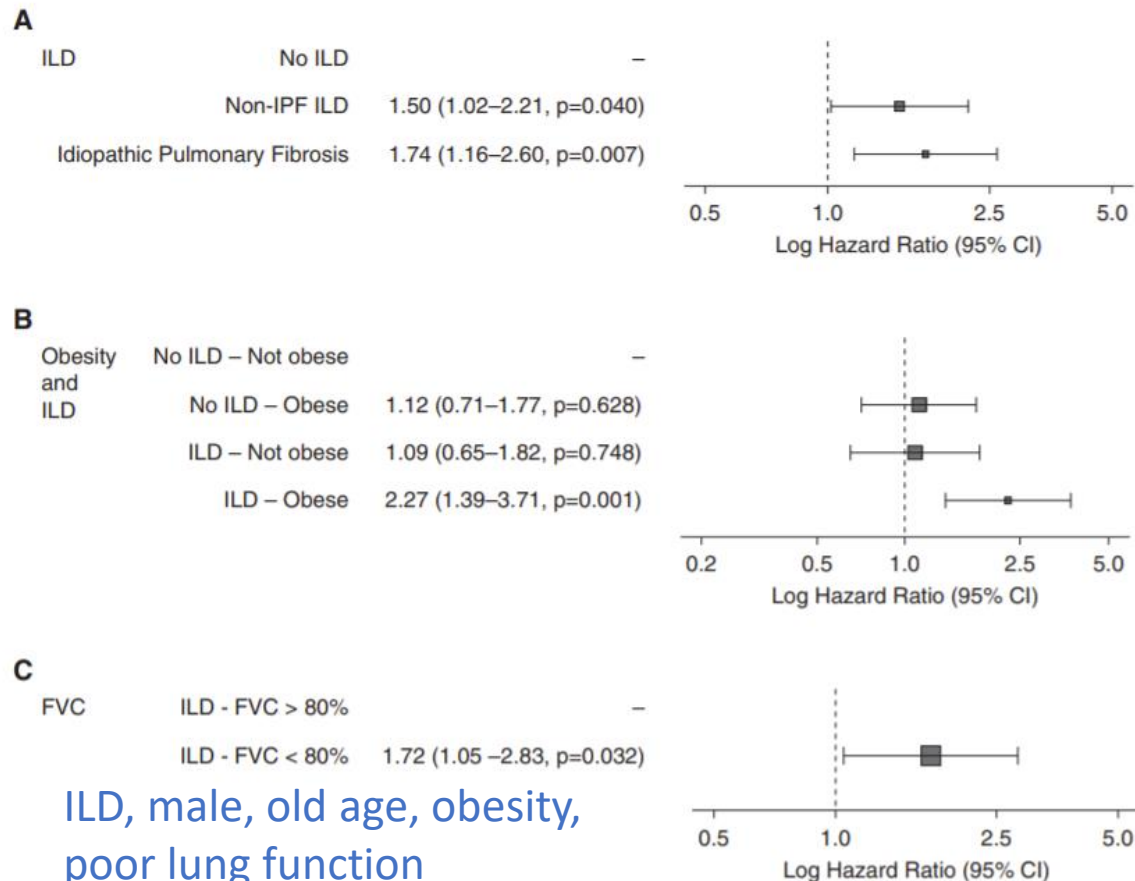
Detection	Total	Sensitivity%	Specificity%	Positive predictive value%	Negative predictive value%	Positive likelihood ratio	Negative likelihood ratio	Youden's Index
RT-PCR	568	78.2(68/87)	98.8(475/481)	91.9(68/74)	96.2(475/494)	65.17	0.221	0.770
CT ^a	364	66.7(54/81)	68.2(193/283)	56.8(54/95)	92.3(193/209)	2.10	0.488	0.343
RT&RT	241	86.2(75/87)	93.5(144/154)	88.2(75/85)	92.3(144/156)	13.26	0.148	0.797
RT&CT ^a	370	91.4(74/81)	66.8(189/283)	62.2(74/119)	97.9(189/193)	2.75	0.129	0.581

^a 60 cases manifested uncertain CT scan results, including 11 COVID-19 patients and 49 non-COVID-19 ones.

Outcome of COVID-19 in Patients with ILD

Patients with ILD submitted to audit
n=371

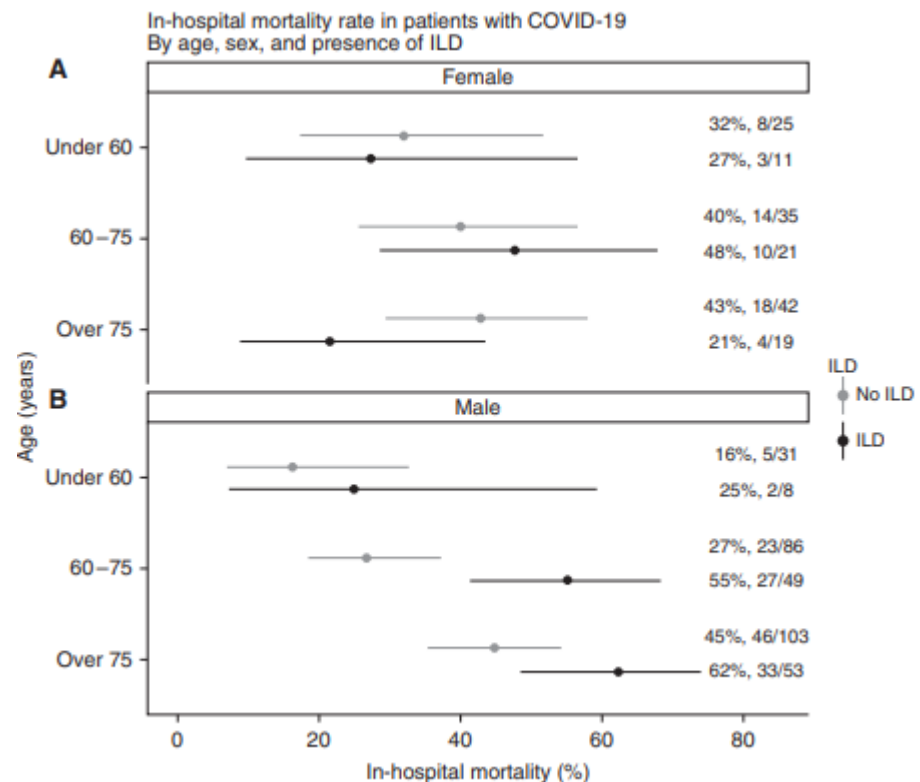
Survival (mortality): HR (95% CI, p-value)



ILD, male, old age, obesity, poor lung function

Table 2. Outcomes by ILD

	Total (n)	No ILD	ILD	P Value
Died	483	114 (35.4)	79 (49.1)	0.013
Respiratory support	483			
Unenhanced respiratory support*		254 (78.9)	136 (84.5)	0.288
Enhanced respiratory support		39 (12.1)	20 (12.4)	—
Ventilation		29 (9.0)	6 (3.7)	—
Length of stay for those alive, median (IQR)	290	9.0 (11.0)	10.0 (8.0)	0.725 [†]



Risk factors for mortality after COVID-19 infection in Patients with ILD

Survey March-May 2020 in ILD centers in France

N = 123 with preexisting ILD who developed COVID-19

30d mortality

N = 48 had fibrotic idiopathic ILD

17 (35%)

N = 75 other ILDs

14 (19%)

	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Sex, M/F	4.22 (1.47–12.06)	0.01	3.90 (1.17–13.04)	0.03
Age, yr	1.07 (1.03–1.10)	<0.01	1.07 (1.04–1.11)	<0.01
Body mass index, kg · m ⁻²	1.02 (0.96–1.09)	0.51	—	—
Underlying ILD, fibrotic/other	2.15 (1.06–4.35)	0.04	—	—
Comorbidities, yes/no				
Obesity	1.01 (0.41–2.47)	0.99	—	—
Hypertension	2.48 (1.18–5.21)	0.02	—	—
Cardiovascular disease	3.20 (1.55–6.59)	<0.01	—	—
Diabetes mellitus	1.46 (0.69–3.06)	0.32	—	—
Chronic kidney disease	1.81 (0.63–5.20)	0.27	—	—
Cancer or hemopathy	3.21 (1.12–9.21)	0.03	5.82 (1.88–18.08)	<0.01
Pulmonary hypertension	2.88 (1.22–6.83)	0.02	—	—
Pulmonary characteristics				
FVC% predicted	0.98 (0.96–0.99)	0.02	—	—
Corrected DL _{CO} % predicted	0.96 (0.94–0.99)	<0.01	—	—
Oxygen supplementation at home	4.25 (2.02–8.91)	<0.01	4.56 (2.13–9.78)	<0.01
Treatment at baseline, yes/no				
Antifibrotic medication	3.09 (1.27–7.55)	0.01	—	—
Glucocorticoids	1.06 (0.51–2.18)	0.88	—	—
Immunosuppressive drugs	0.58 (0.26–1.30)	0.19	—	—
COVID-19-related medications, yes/no				
Any	1.43 (0.70–2.92)	0.32	—	—
Lopinavir/ritonavir	1.61 (0.49–5.30)	0.43	—	—
Azithromycine	0.23 (0.03–1.72)	0.15	—	—
Hydroxychloroquine	1.58 (0.60–4.11)	0.35	—	—
Glucocorticoids	1.15 (0.40–3.28)	0.80	—	—

Treatment; systemic corticosteroids

▶ Mechanically ventilated patients with COVID-19 who have ARDS

- Decreased risk of death in those treated with methylprednisolone (hazard ratio, 0.38; 95% CI, 0.20- 0.72)

▶ Severe acute respiratory syndrome

- Early use of hydrocortisone was associated with higher plasma viral load and delayed viral clearance
- Similar results in Middle East respiratory syndrome

▶ Acute exacerbation of ILD

- Prudent to avoid early use of corticosteroids in patients with ILD and COVID-19
- Corticosteroids are likely appropriate in the presence of ongoing inflammatory findings on chest imaging after resolution of the initial infection
- Risks: delayed virus clearance, secondary infections, drug interactions → temporary discontinuation of other immunomodulatory therapies

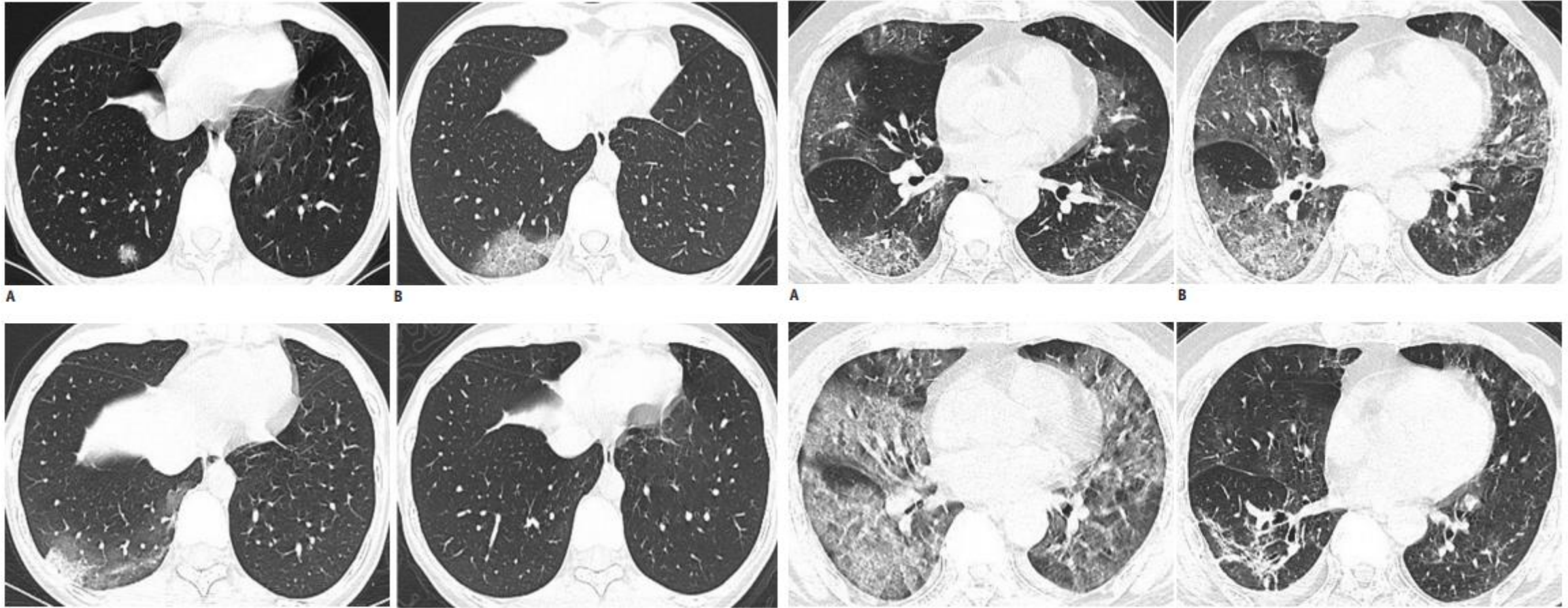
Nonpharmacologic treatment

- ▶ Low lung volume and low driving pressure ventilation strategies
- ▶ Higher PEEP (> 10 cm H₂O), with close monitoring for barotrauma ↔ Concern about worsening hemodynamic impairment
 - Higher PEEP strategy is associated with increased 1Y mortality (HR, 4.72; 95% CI, 2.06-11.15) in patients with fibrotic ILD and is preferably avoided
 - In-hospital mortality for patients with an exacerbation of IPF is estimated at 50%
 - The mortality rate for patients with COVID-19 requiring mechanical ventilation has ranged from 61% to as high as 97%
- ▶ Mechanical ventilation in patients with fibrotic ILD and concurrent COVID-19 may not be appropriate

Brief summary; COVID-19 in patients with IPF

- ▶ The risk of COVID-19 is high
 - Older age, Male, Cardiovascular comorbidities
- ▶ Antifibrotic treatment seems to have no impact on the risk of severity of COVID-19
 - It is recommended to continue treatment
- ▶ Acute exacerbations
 - May often be triggered by respiratory infections, especially viral
 - Difficult to differentiate acute exacerbation from pneumonia due to COVID-19

Pulmonary fibrosis after COVID-19



Case #1 (22/F)
fever

Case #2 (M/72)
fever, myalgia, ICU care +

Pulmonary fibrosis after COVID-19

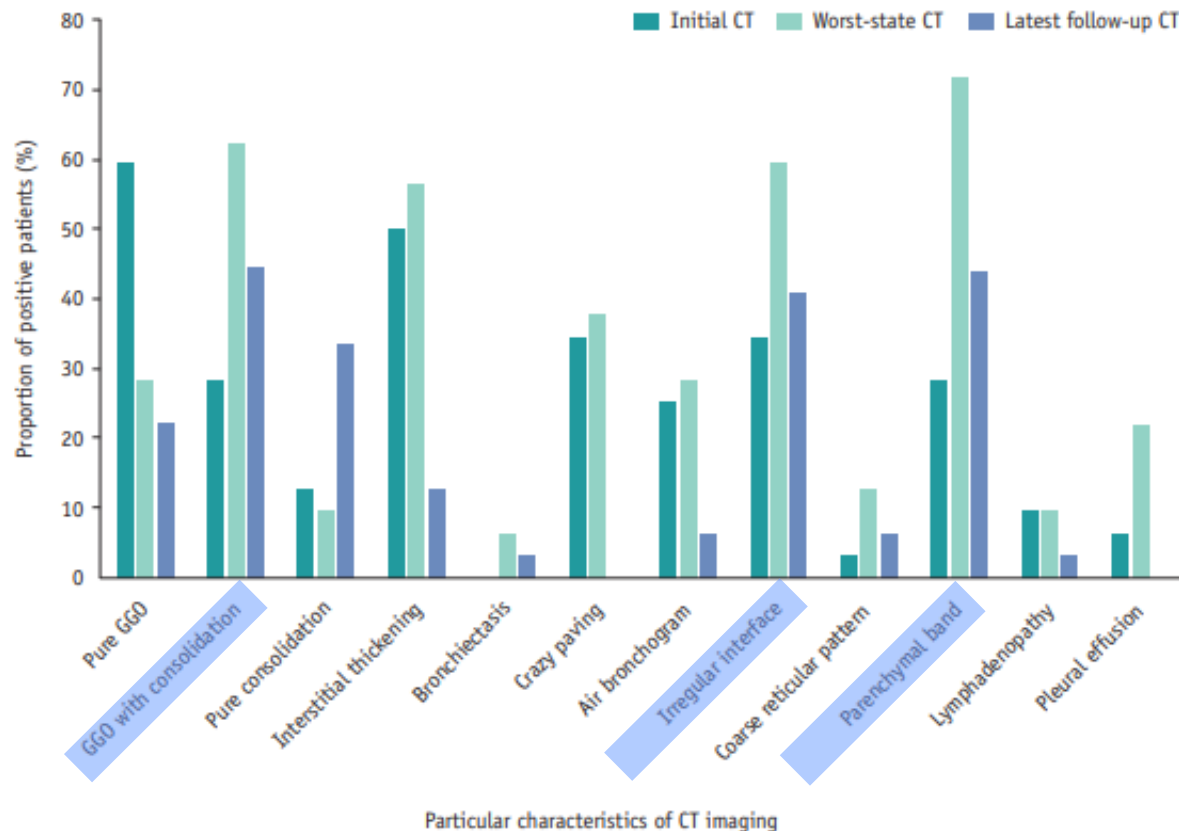


Table 4. Comparison of Particular Characteristics between Groups on Worst-State CT Imaging

Characteristic	Initial CT		p	Worst-State CT		p
	Fibrosis Group (n = 14)	Non-Fibrosis Group (n = 18)		Fibrosis Group (n = 14)	Non-Fibrosis Group (n = 18)	
Number of affected segments	11.0 (4.0–13.0)	3.5 (1.0–10.0)	0.040	14.0 (11.8–18.0)	6.5 (3.0–11.3)	< 0.001
Location*						
Upper lobe	11 (78.6)	8 (44.4)		14 (100)	10 (55.6)	
Middle lobe or lingula	11 (78.6)	5 (27.8)		14 (100)	5 (27.8)	
Lower lobe	13 (92.9)	16 (88.9)		14 (100)	17 (94.4)	
Bilateral lobes	11 (78.6)	12 (66.7)		14 (100)	14 (77.8)	
Distribution						
Central	0 (0)	0 (0)	0.165	0 (0)	0 (0)	0.124
Peripheral	4 (28.6)	10 (71.4)		2 (14.3)	8 (44.4)	
Both central and peripheral [†]	10 (55.6)	8 (44.4)		12 (85.7)	10 (55.6)	
Opacification						
Pure GGO	9 (64.3)	10 (55.6)	0.714	4 (28.6)	5 (27.8)	0.929
GGO with consolidation	4 (28.6)	5 (27.8)		9 (64.3)	11 (61.1)	
Pure consolidation	1 (7.1)	3 (16.7)		1 (7.1)	2 (11.1)	
Interstitial thickening	8 (57.1)	8 (44.4)	0.722	11 (78.6)	7 (38.9)	0.036
Bronchiectasis	0 (0)	0 (0)	-	2 (14.3)	0 (0)	0.183
Mosaic attenuation	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Crazy paving	6 (42.9)	5 (27.8)	0.465	6 (42.9)	6 (33.3)	0.718
Air bronchogram	6 (42.9)	2 (11.1)	0.096	8 (57.1)	1 (5.6)	0.004
Irregular interface	8 (57.1)	3 (16.7)	0.027	12 (85.7)	7 (38.9)	0.012
Coarse reticular pattern	1 (7.1)	0 (0)	0.437	4 (28.6)	0 (0)	0.028
Parenchymal band	7 (50.0)	2 (11.1)	0.022	13 (92.9)	10 (55.6)	0.044
Lymphadenopathy	3 (21.4)	0 (0)	0.073	3 (21.4)	0 (0)	0.073
Pleural effusion	2 (14.3)	0 (0)	0.183	6 (42.9)	1 (5.6)	0.027

► Irregular interface and parenchymal band could predict the formation of pulmonary fibrosis early

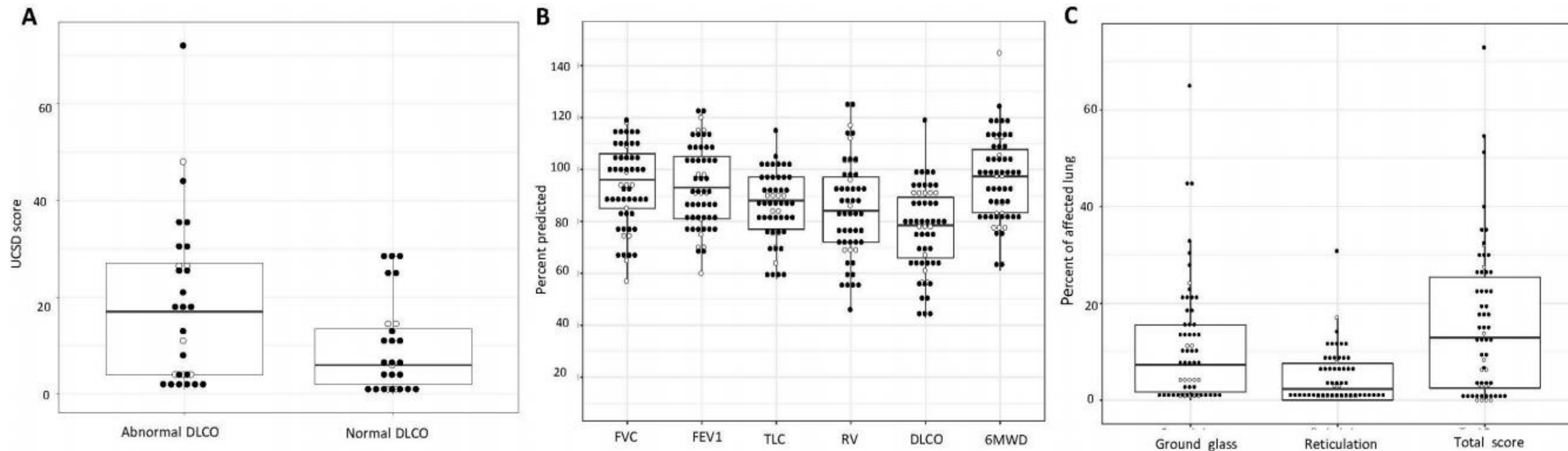
Abnormal pulmonary function in COVID-19 patients

► At time of hospital discharge

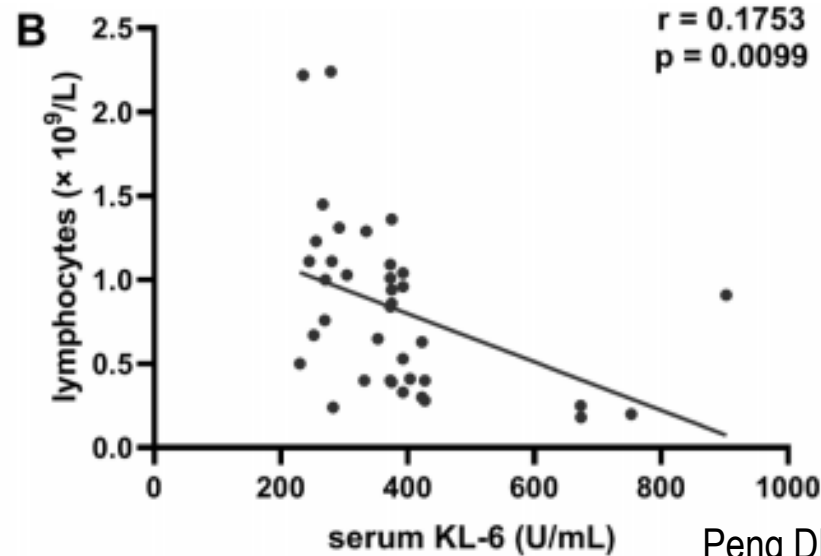
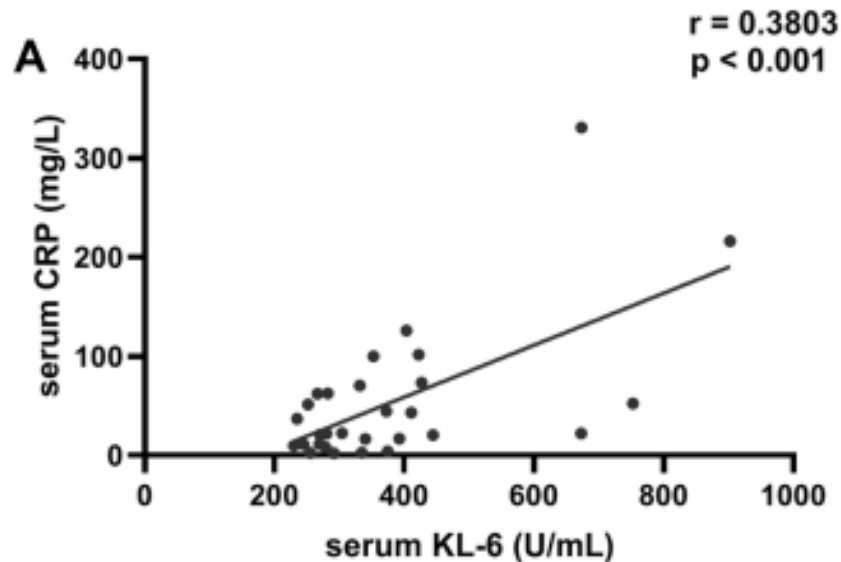
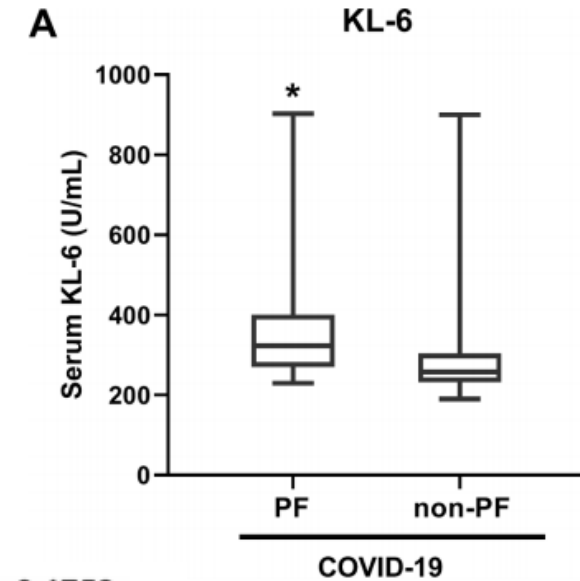
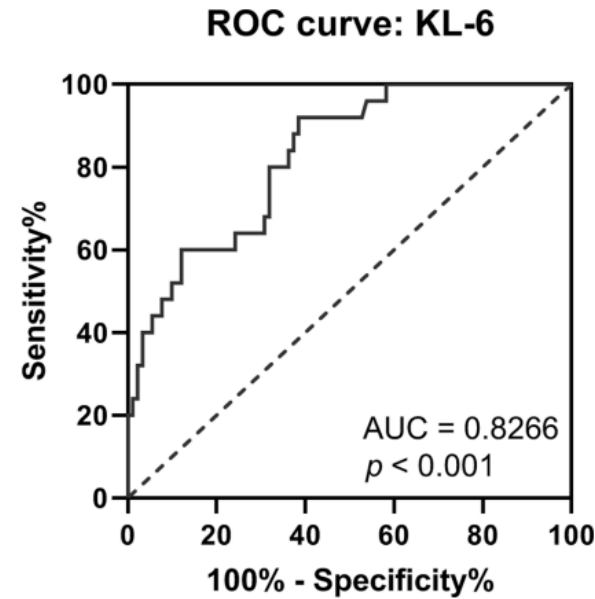
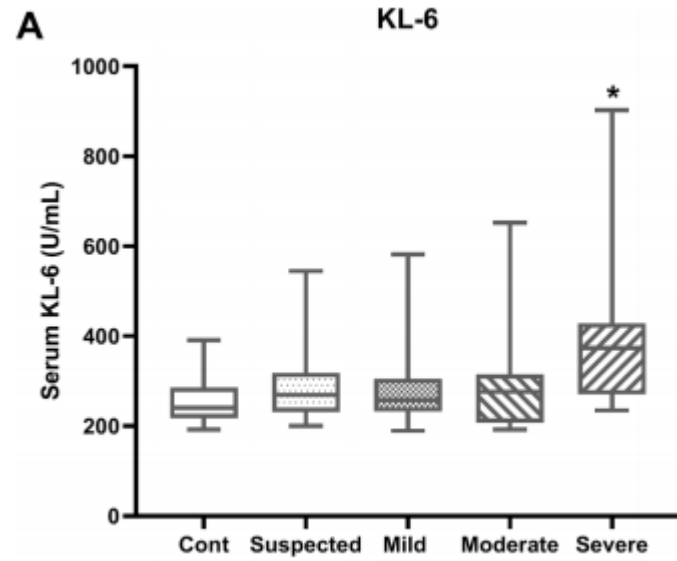
	Total (n=110)	Mild illness (n=24)	Pneumonia (n=67)	Severe Pneumonia (n=19)	p value		Total (n=110)	Mild illness (n=24)	Pneumonia (n=67)	Severe Pneumonia (n=19)	p value
Age, years	49.1 ± 14.0	46.8 ± 15.6	47.9 ± 13.7	56.5 ± 11.0 ^{a,b}	0.04	Diffusion capacity					
Female	55 (50.0%)	13 (54.2%)	36 (53.7%)	6 (31.6%)	0.21	DLCO%pred	78.18 ± 14.29	84.70 ± 13.88	79.76 ± 11.99	64.79 ± 14.35 ^{a,b}	<0.001
Smoker	13 (11.8%)	4 (16.7%)	7 (10.4%)	2 (10.5%)	0.707	<80%pred, No.(%)	51 (47.22)	7 (30.43)	28 (42.42)	16(84.21) ^{a,b}	0.001
BMI	23.5 ± 3.0	23.1 ± 2.8	23.6 ± 3.2	23.5 ± 2.7	0.794	DLCO/VA%pred	92.09 ± 16.68	99.35 ± 18.25	92.30 ± 15.70	82.58 ± 13.91 ^{a,b}	0.004
Duration (onset to discharge)	27±9	20±6	29±8 ^a	34±7 ^{a,b}	<0.001	<80%pred, No.(%)	29 (26.85)	3 (13.04)	18 (27.27)	8 (42.11)	0.09
Underlying disease	44 (40.0%)	10 (41.7%)	25 (37.3%)	9 (47.4%)	0.719	Lung volume					
Lung disease	3 (2.7%)	0 (0%)	3 (4.5%)	0 (0%)	1	TLC%pred	86.32 ± 11.32	87.13 ± 10.43	88.11 ± 10.72	79.16 ± 12.13 ^{a,b}	0.008
Spirometry						<80%pred, No.(%)	27 (25.00)	4 (17.39)	14 (21.21)	9 (47.37) ^{a,b}	0.049
FVC%pred	93.59 ± 12.25	94.06 ± 10.48	94.12 ± 12.31	91.12 ± 14.30	0.632	RV%pred	86.83 ± 19.37	87.17 ± 16.88	89.79 ± 19.21	76.16 ± 19.96 ^b	0.024
<80% pred, No.(%)	10 (9.09)	3 (12.50)	5 (7.46)	2 (10.53)	0.644	<65%pred, No.(%)	10 (9.26)	2 (8.70)	3 (4.55)	5 (26.32) ^b	0.021
FEV ₁ %pred	92.70 ± 11.57	94.26 ± 11.00	92.59 ± 11.87	91.12 ± 11.58	0.676	RV/TLC%pred	96.99 ± 16.72	98.00 ± 14.93	98.53 ± 17.55	90.42 ± 14.86	0.168
<80% pred, No.(%)	15 (13.64)	4 (16.67)	9 (13.43)	2 (10.53)	0.857						

Risk of developing lung function impairment

- ▶ Pulmonary and radiological function abnormalities that persist in previously hospitalized patients assessed 12 weeks after COVID-19 symptom onset
 - Abnormal pulmonary function variable : 58%
 - Abnormal imaging on chest CT : 88%



Correlation of KL-6 with pulmonary fibrosis in COVID-19



Systemic corticosteroids

Table 5: Follow up data from patients with interstitial lung disease following infection with SARS-CoV-2. Data are presented as percentage value or mean \pm standard deviation (SD) unless otherwise stated. FEV1: Forced Expiratory Volume in 1s; FVC: Forced Vital Capacity; TLCO: Transfer Factor of the lung for Carbon Monoxide; KCO: Transferr Coefficient

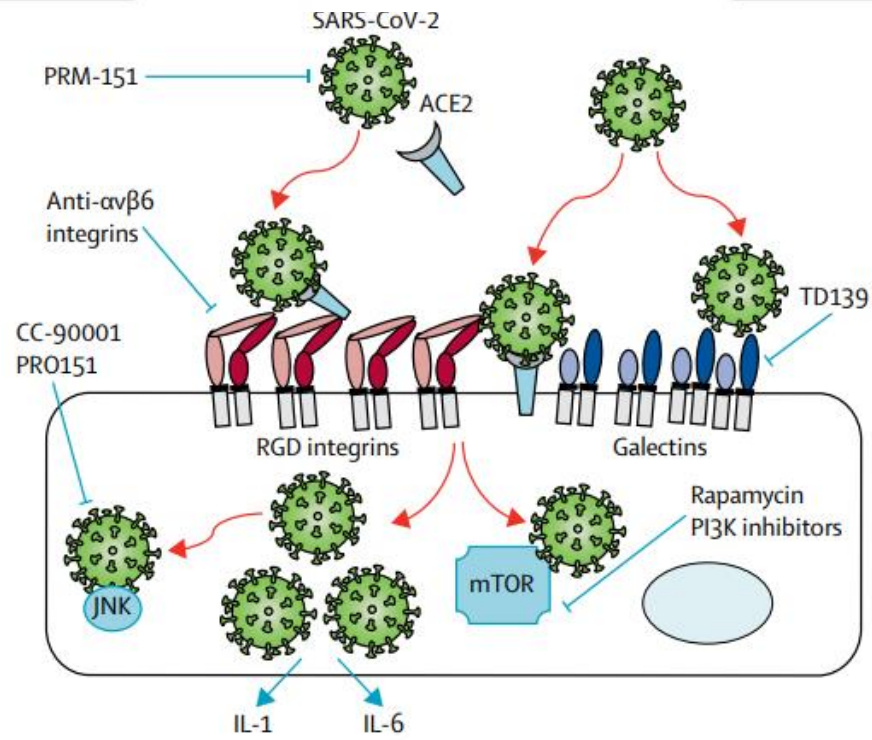
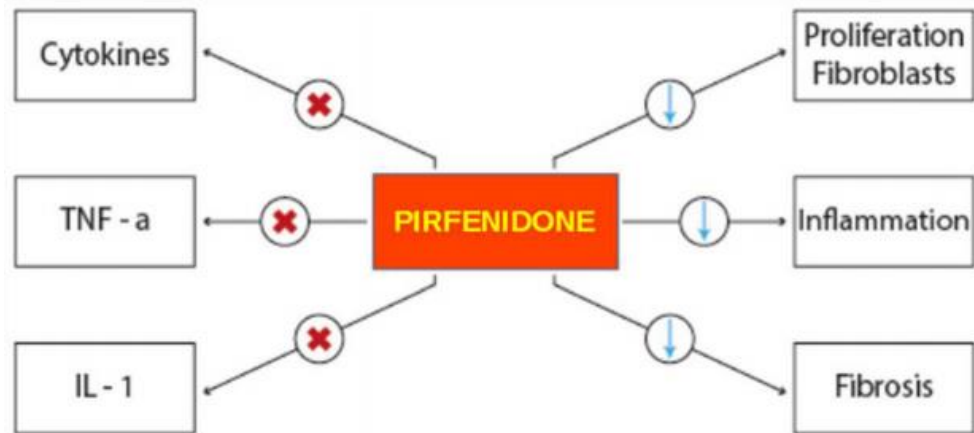
n = 30	Pre-treatment	Post-treatment	Mean difference (95% CI)	p
FVC (L)	3.07 \pm 1.12	3.36 \pm 1.11	0.42 (0.28 – 0.56)	0.014
FVC (%)	86.8 \pm 18.5	99.2 \pm 19.1	9.63 (4.49 –14.7)	0.004
TLCO (SI)	5.56 \pm 2.56	7.05 \pm 2.42	1.72 (1.18 – 2.25)	<0.001
TLCO (%)	59.7 \pm 21.1	82.6 \pm 15.7	22.3 (14.1-32.5)	<0.001
KCO (TLCO/L)	1.25 \pm 0.34	1.83 \pm 0.36	0.27 (0.16-0.37)	0.025
KCO (%)	82.9 \pm 28.8	104.3 \pm 24.0	19.9 (9.72-30.1)	0.002

► Screened for sequelae of SARS-CoV2 pneumonitis (N=837)

- Significant functional deficit: 35/837 survivor (4.8%)
- Patients received steroid treatment (n=30)

► Early treatment with corticosteroids was well tolerated and associated with rapid and significant improvement

Antifibrotic agents



	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

Vitiello A, et al. *SN Compr. Clin. Med.* 2020;2:1709–1712.

George PM, et al. *Lancet Respir Med* 2020; 8: 807–15.

ILD and COVID-19 vaccination



Pulmonary fibrosis patients should be given priority in COVID-19 vaccination programmes: A Joint Statement

- ▶ There are no long-term data available
- ▶ Can be used safely in patients with rheumatic and musculoskeletal diseases
- ▶ Preferably be given when the disease is in a stable phase
- ▶ Preferred to provide the vaccine before planned immunosuppressive treatment
- ▶ Vaccination can be performed regardless of immunosuppressive treatment

Table 3 Clinical risk groups 16 years of age and over who should receive COVID-19 immunisation.

Chronic respiratory disease	Individuals with a severe lung condition, including those with asthma that requires continuous or repeated use of systemic steroids or with previous exacerbations requiring hospital admission, and chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, <u>interstitial lung fibrosis</u> , pneumoconiosis and bronchopulmonary dysplasia (BPD).
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Research in ILD during pandemic

Impact	Potential Strategies for Mitigation
Work-from-home mandates for nonessential employees	<ul style="list-style-type: none">• Support remote access for all employees• Reallocate research staff and trainees to projects that can be worked on remotely (eg, electronic chart reviews)• Establish regular virtual laboratory meetings by video conference
Restrictions on in-person study visits	<ul style="list-style-type: none">• Modification of study protocols to waive completion of nonessential efficacy endpoints• Modification of study protocols to allow virtual visits• Use statistical analyses that are less prone to bias from missing data
Interrupted recruitment	<ul style="list-style-type: none">• Maintain list of potential trial participants• Consider potential biases introduced by interrupted recruitment (eg, changing treatment patterns, unequal season of enrollment)• Adjust for timing of enrollment (eg, pre- vs postinterruption) in statistical analyses
Reduced access to study medications	<ul style="list-style-type: none">• Coordinate with study sponsors and local research ethics boards to have study drug delivered (temperature controlled) directly to patients rather than dispensed by hospital-based pharmacies
Decreased clinical trial revenue and risk to research staff salaries	<ul style="list-style-type: none">• Reallocate research staff to projects that have ongoing funding and can be worked on remotely• Work to establish short-term funding support from trial sponsors, research institution, hospital, etc.
Cancelled/postponed grant competitions	<ul style="list-style-type: none">• Consider synergies of existing research programs with calls for COVID-19 funding applications

Summary

▶ Patients with ILD are at risk of severe COVID-19

▶ Diagnosis

- Defer non-essential appointments
- Perform surgical lung biopsy, bronchoscopy and PFTs only in cases when it is really needed

▶ Treatment

- Follow general preventive measures
- Continue treatment, especially antifibrotic therapy, as prescribed to minimize the risk of the underlying disease getting worse (caution with use of high-dose corticosteroids)
- Monitor closely the adverse events and the efficacy; telephone consultation, home monitoring
- Vaccination should be performed as soon as the vaccine is available

감사합니다
Thank you!

