Long-Haul COVID: Problems and Opportunities

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Disclosures

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Learning Objectives

Identify the key organ system characteristics of long COVID patients experiencing pulmonary/cardiovascular symptoms.

Understand the presentation and treatment of pulmonary symptoms in long COVID

Identify the management and care approaches for the physical (pulmonary/cardiovascular) symptoms of long COVID.

Describe the diagnostic, management, and treatment pathways for patients in a post-COVID care clinic, including how patients are referred to/connected with the clinic.

“Victory comes **from finding opportunities in problems**..”

Sun Tzu

Problem 1: Case Definitions Vary

- Various names in the literature: “long COVID,” “post-COVID syndrome,” “post-acute COVID-19 syndrome,” as well as the research term “post-acute sequelae of SARS-CoV-2 infection” (PASC).
- Heterogenous clinical presentation
- Unknown natural history of disease

Long Haul COVID Can Effect Almost Every Organ System

Acute Complications of COVID-19

Neuropsychiatric
- Cerebrovascular accident
- Large vessel disease
- Encephalopathy, delirium
- Anosmia, ageusia

Respiratory
- Pneumonia
- Hypoxemic respiratory failure, ARDS

Cardiovascular
- Arrhythmia
- Myocarditis

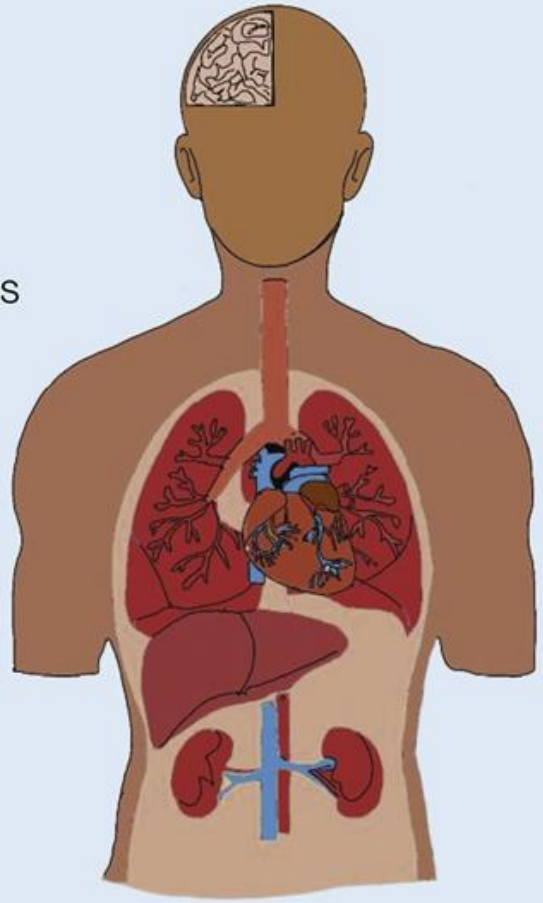
Hematologic, Vascular
- Coagulopathy
- Thrombotic events

Renal
- Acute kidney injury

Gastrointestinal, Hepatobiliary
- Diarrhea
- Acute liver injury

Musculoskeletal
- Rhabdomyolysis

Dermatologic
- Livedo reticularis
- Maculopapular or urticarial rash



Post-COVID Symptoms, Sequelae

Neuropsychiatric
- Neurocognitive deficits
- Mood changes
- Sensory & motor deficits
- Chronic fatigue and sleep disruption

Respiratory
- Persistent dyspnea
- Chronic cough

Cardiovascular
- Chest pain
- Palpitations

Hematologic, Vascular
- Persistent or recurrent thrombosis

Renal
- Chronic kidney disease

Gastrointestinal, Hepatobiliary
- Persistent liver dysfunction

Musculoskeletal
- Muscle wasting
- Weakness
- Deconditioning

Dermatologic
- Hair loss

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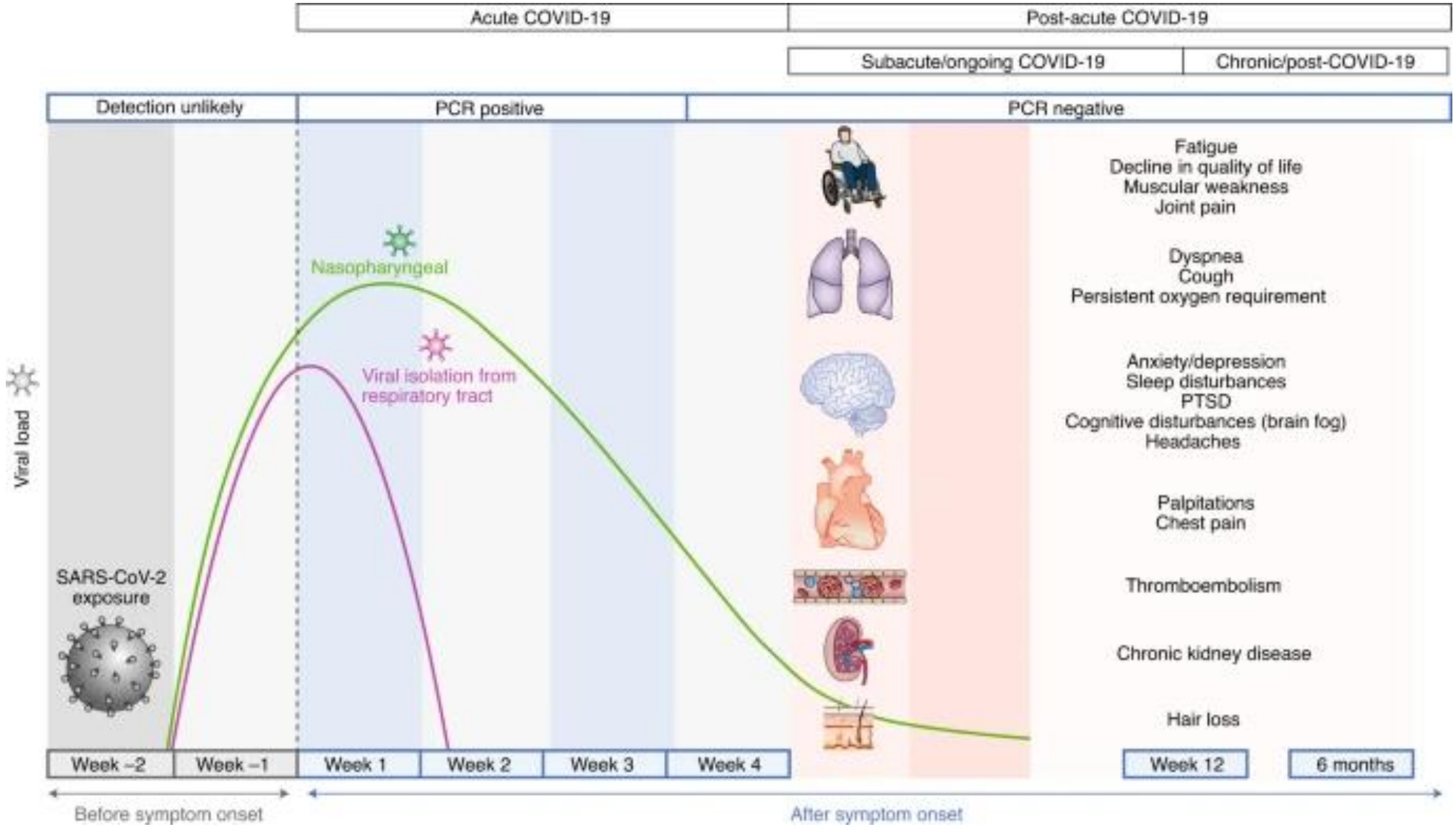
Lutchmansingh DD, Knauert MP, Antin-Ozerkis DE, Chupp G, Cohn L, Dela Cruz CS, Ferrante LE, Herzog EL, Koff J, Rochester CL, Ryu C, Singh I, Tickoo M, Winks V, Gulati M, Possick JD. A Clinic Blueprint for Post-Coronavirus Disease 2019 RECOVERY: Learning From the Past, Looking to the Future. Chest. 2021 Mar;159(3):949-958. doi: 10.1016/j.chest.2020.10.067. Epub 2020 Nov 4. PMID: 33159907; PMCID: PMC7641526.



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Type, proportion, and duration of persistent COVID-19 symptoms*

Persistent symptom ¶	Proportion of patients affected by symptom	Approximate time to symptom resolution Δ
Common physical symptoms		
Fatigue	15 to 87%[1,2,6,9,14]	3 months or longer
Dyspnea	10 to 71%[1,2,6-9,14]	2 to 3 months or longer
Chest discomfort	12 to 44%[1,2]	2 to 3 months
Cough	17 to 34%[1,2,9,12]	2 to 3 months or longer
Anosmia	10 to 13%[1,3-5,9,11]	1 month, rarely longer
Less common physical symptoms		
Joint pain, headache, sicca syndrome, rhinitis, dysgeusia, poor appetite, dizziness, vertigo, myalgias, insomnia, alopecia, sweating, and diarrhea	<10%[1,2,8,9,11]	Unknown (likely weeks to months)
Psychologic and neurocognitive		
Post-traumatic stress disorder	7 to 24%[6,10, 14]	6 weeks to 3 months or longer
Impaired memory	18 to 21%[6,15]	weeks to months
Poor concentration	16%[6]	Weeks to months
Anxiety/depression	22 to 23%[2,7,8,10, 12,13, 14]	Weeks to months
Reduction in quality of life	>50%[8]	Unknown (likely weeks to months)

COVID-19: coronavirus disease 2019.

* These data are derived from an earlier period in the pandemic; information on patient recovery and persistent symptoms is evolving, and these figures may change as longer-term data emerge.

¶ More than a third of patients with COVID-19 experience **more than one** persistent symptom.

Δ Time course for recovery varies depending on premorbid risk factors and illness severity and may be shorter or longer than that listed. Hospitalized patients, and in particular critically ill patients, are more likely to have a more protracted course than

Mikkelsen ME, Abramoff B. **COVID-19: Evaluation and management of adults following acute viral illness**In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on October 22, 2021.)

Opportunity 1:
Recognition of the need for case definition flexibility

CDC Defines Post-Covid Conditions:

"We use **post-COVID conditions** as an **umbrella term** for the wide **range of health consequences** that are present **four or more weeks after infection with SARS-CoV-2.** The time frame of four or more weeks provides a rough approximation of effects that occur beyond the acute period, but the timeframe might change as we learn more."

Problem 2: Case presentation and severity of post-covid symptoms may not be related to severity of initial illness

- Despite early data suggesting 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, more recent studies have found that this does not always hold true.

- In addition three separate recent studies have found that while many patients have persistent symptoms 4 weeks after discharge, many of these patients have no objective evidence of physiologic or radiographic abnormalities

- The preponderance of published studies have been in patients who have been hospitalized with COVID- and there is a dearth of data on long term outcomes of non-hospitalized patients with persistent symptoms

Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, Preston R, Thillai M, Dewar A, Molyneaux PL, West AG. Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment. Ann Am Thorac Soc. 2021 May;18(5):799-806. doi: 10.1513/AnnalsATS.202008-1002OC. PMID: 33433263; PMCID: PMC8086530.

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In discharged patients post COVID 19 relatively normal oxygen saturations can be demonstrated However with PFT testing the most common abnormality of lung function is impairment of diffusion capacity

	Total	Mild illness	Pneumonia	Severe pneumonia	p-value
Patients	110	24	67	19	
Age years	49.1±14.0	46.8±15.6	47.9±13.7	56.5±11.0*,#	0.04
Female	55 (50.0)	13 (54.2)	36 (53.7)	6 (31.6)	0.21
Smoker	13 (11.8)	4 (16.7)	7 (10.4)	2 (10.5)	0.707
BMI kg·m^{-2}	23.5±3.0	23.1±2.8	23.6±3.2	23.5±2.7	0.794
Duration from onset to discharge days	27±9	20±6	29±8**	34±7**,#	<0.001
S_{pO_2} on discharge %	98.7±1.0	98.6±1.2	98.7±1.0	98.5±1.0	0.73
Spirometry					
FVC % pred	93.59±12.25	94.06±10.48	94.12±12.31	91.12±14.30	0.632
FVC <80% pred	10 (9.09)	3 (12.50)	5 (7.46)	2 (10.53)	0.644
FEV_1 % pred	92.70±11.57	94.26±11.00	92.59±11.87	91.12±11.58	0.676
FEV_1 <80% pred	15 (13.64)	4 (16.67)	9 (13.43)	2 (10.53)	0.857
FEV_1/FVC %	80.70±5.81	81.84±5.48	80.39±6.12	80.19±5.15	0.509
FEV_1/FVC <70%	5 (4.55)	0 (0)	5 (7.46)	0 (0)	0.349
MMEF % pred	97.40±26.23	99.77±28.17	96.59±26.51	96.14±23.82	0.879
MMEF <65% pred¶	7 (6.42)	1 (4.17)	6 (9.09)	0 (0)	0.551
$FEF_{50\%}$ % pred	94.74±26.11	97.47±25.48	94.09±26.80	93.53±25.56	0.845
$FEF_{50\%}$ <65% pred¶	12 (11.01)	2 (8.33)	8 (12.12)	2 (10.53)	1
$FEF_{75\%}$ % pred	96.10±32.56	102.23±40.20	95.02±30.89	92.08±27.92	0.549
$FEF_{75\%}$ <65% pred¶	12 (11.01)	3 (12.50)	4 (6.06)	5 (26.32)#	0.035
Diffusion capacity					
D_{LCO} % pred	78.18±14.29	84.70±13.88	79.76±11.99	64.79±14.35**,##	<0.001
D_{LCO} <80% pred	51 (47.22)	7 (30.43)	28 (42.42)	16 (84.21)**,##	0.001
D_{LCO}/V_A % pred	92.09±16.68	99.35±18.25	92.30±15.70	82.58±13.91**,#	0.004
D_{LCO}/V_A <80% pred	29 (26.85)	3 (13.04)	18 (27.27)	8 (42.11)	0.09
Lung volume					
TLC % pred	86.32±11.32	87.13±10.43	88.11±10.72	79.16±12.13*,##	0.008
TLC <80% pred	27 (25.00)	4 (17.39)	14 (21.21)	9 (47.37)*,#	0.049
RV % pred	86.83±19.37	87.17±16.88	89.79±19.21	76.16±19.96##	0.024
RV <65% pred	10 (9.26)	2 (8.70)	3 (4.55)	5 (26.32)#	0.021
RV/TLC % pred	96.99±16.72	98.00±14.93	98.53±17.55	90.42±14.86	0.168

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Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, Lei C, Chen R, Zhong N, Li S. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020 Jun 18;55(6):2001217. doi: 10.1183/13993003.01217-2020. PMID: 32381497; PMCID: PMC7236826.

Opportunity 2: Our understanding of medicine and pulmonary physiology has advanced in the last two years

Variable	Patients Recovered from COVID-19 (n = 10)	Control Participants (n = 10)	*P* Value
Characteristics			
Age, y	48 ± 15	48 ± 8	.87
Female sex	9 (90)	8 (80)	.53
BMI, kg/m^2	28 ± 6	24 ± 6	.11
Hemoglobin, g/dL	13.4 ± 1.1	14.2 ± 1.4	.16
Interval from acute COVID-19 infection to iCPET, mo	11 ± 1	Not applicable	...
Comorbidities			
Systemic hypertension	2 (20)	3 (30)	.61
Diabetes	0	1 (10)	.30
Medications			
β-Adrenergic receptor blocker	1 (5)	1 (5)	1.00
ACE inhibitor or ARB	2 (20)	0	.13
Diuretics	0	1 (10)	.30
Pulmonary function test			
FEV_1, %	97 ± 1	100 ± 1	.34
FVC, %	96 ± 1	104 ± 1	.19
FEV_1 to FVC ratio, %	101 ± 3	98 ± 5	.18
Resting upright right heart catheterization			
SaO_2, %	98 (97-98)	98 (97-98)	.64
MvO_2, %	73 ± 3	66 ± 6	.01
Right atrial pressure, mm Hg	0 (0-1)	3 (0-4)	.35
Stroke volume index, mL/m^2	36.3 ± 10.3	40.3 ± 12.8	.44
Cardiac index, L/min/m^2	3.2 ± 0.6	2.8 ± 0.5	.13
mPAP, mm Hg	8 ± 1	12 ± 3	.002
PAWP, mm Hg	2 ± 2	5 ± 3	.01
PVR, WU	1.13 (0.87-1.52)	1.26 (0.95-2.01)	.44
PA compliance, mL/mm Hg	5.6 ± 2.4	7.7 ± 3.3	.13
SVR index, dynes/s/cm^5/m^2	2,554 ± 880	2,924 ± 487	.26

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Singh I, Joseph P, Heerdt PM, Cullinan M, Lutchmansingh DD, Gulati M, Possick JD, Systrom DM, Waxman AB. Persistent Exertional Intolerance After COVID-19: Insights From Invasive Cardiopulmonary Exercise Testing. Chest. 2021 Aug 11:S0012-3692(21)03635-7. doi: 10.1016/j.chest.2021.08.010. Epub ahead of print. PMID: 34389297; PMCID: PMC8354807

Opportunity 3: Our understanding of medicine and pulmonary physiology has advanced in the last two years

Normal ventilatory repsonses:

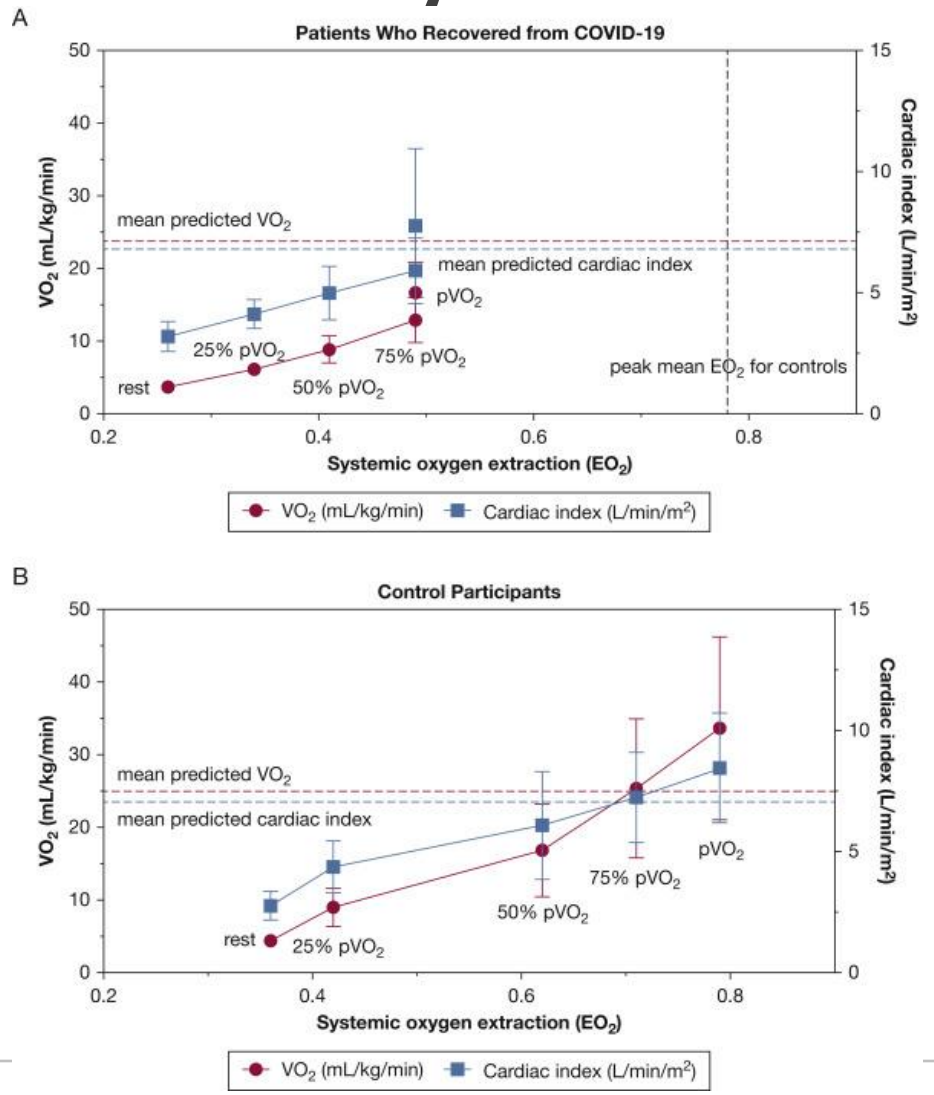
- Respiratory rate increases throughout exercise
- Tidal volume at least doubles over baseline
- Tidal volume reaches 50 to 60% of FVC or 70% of IC
- Breathing reserve 30 to 40%[5]
- VD/VT <0.3 to 0.4 at rest and 0.2 with exercise

Normal cardiovascular responses:

- Heart rate increases linearly with VO_2 up to >90% predicted maximum
- BP increases gradually during exercise, but increase in diastolic pressure <20 mmHg
- Peak oxygen pulse (VO_2/HR) >80% predicted and does not plateau early
- AT occurs at >40% of predicted maximal VO_2
- Nadir of V_E/VCO_2 is <34 or slope of V_E versus VCO_2 <32
- No evidence of arrhythmia or ischemic changes on ECG

Normal gas exchange responses:

- SaO_2 >96% at rest and minimal or no decrease with exercise
- A-a O_2 difference with exercise <35



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Treatment possibility 1: What do we do with our Corticosteroids?

Lung Function	Before Treatment	After Treatment	Mean Difference (95% CI)	*P* Value
FVC, L	3.07 ± 1.12	3.36 ± 1.11	0.42 (0.28–0.56)	0.014
FVC, %	86.8 ± 18.5	99.2 ± 19.1	9.63 (4.49–14.7)	0.004
T_{LCO}, SI	5.56 ± 2.56	7.05 ± 2.42	1.72 (1.18–2.25	<0.001
T_{LCO}, %	59.7 ± 21.1	82.6 ± 15.7	22.3 (14.1–32.5)	<0.001

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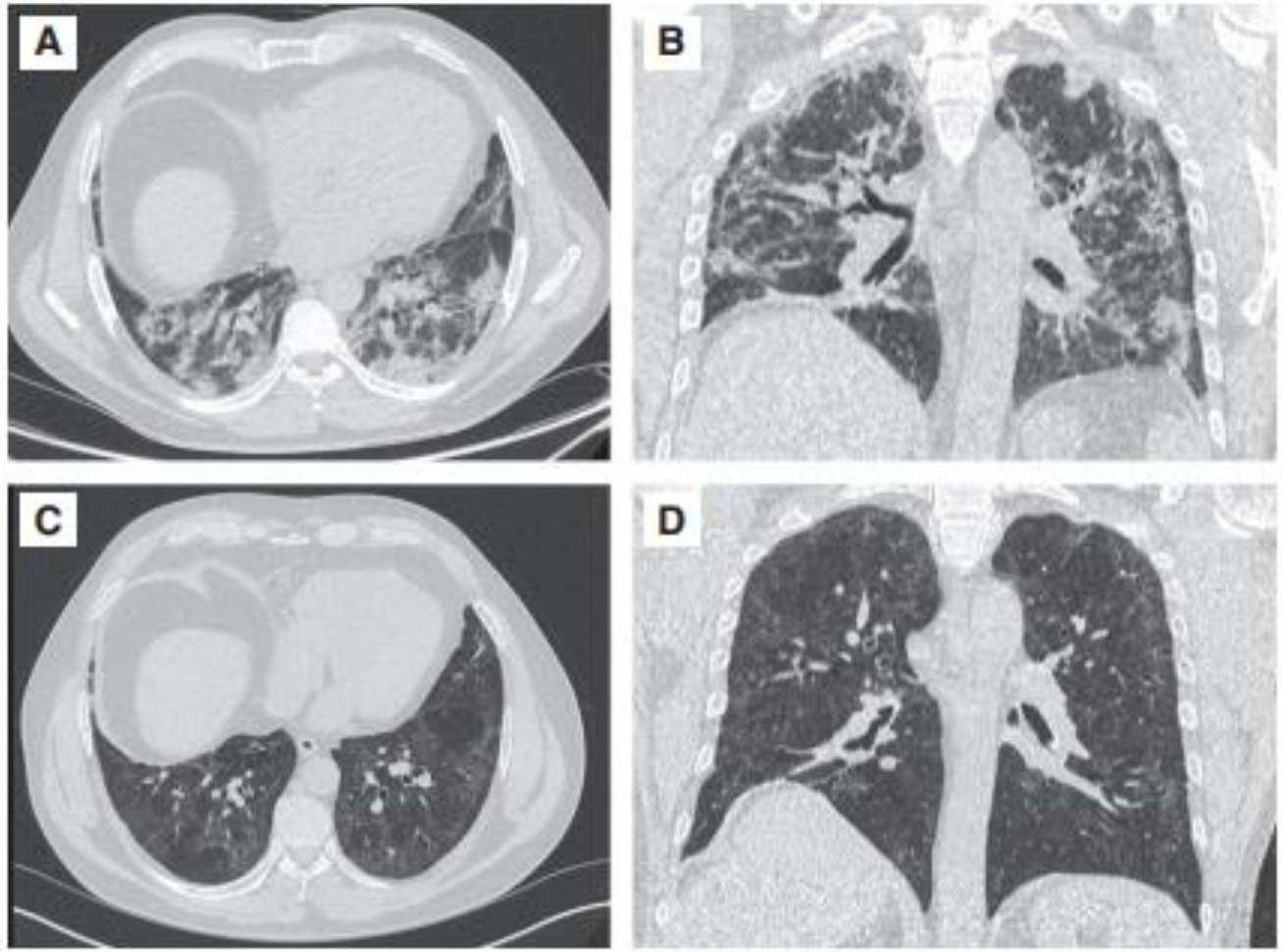
Myall KJ, Mukherjee B, Castanheira AM, Lam JL, Benedetti G, Mak SM, *et al.* Persistent post–COVID-19 interstitial lung disease: an observational study of corticosteroid treatment. *Ann Am Thorac Soc* 2021;18: 799–806.

Improvement Is Possible



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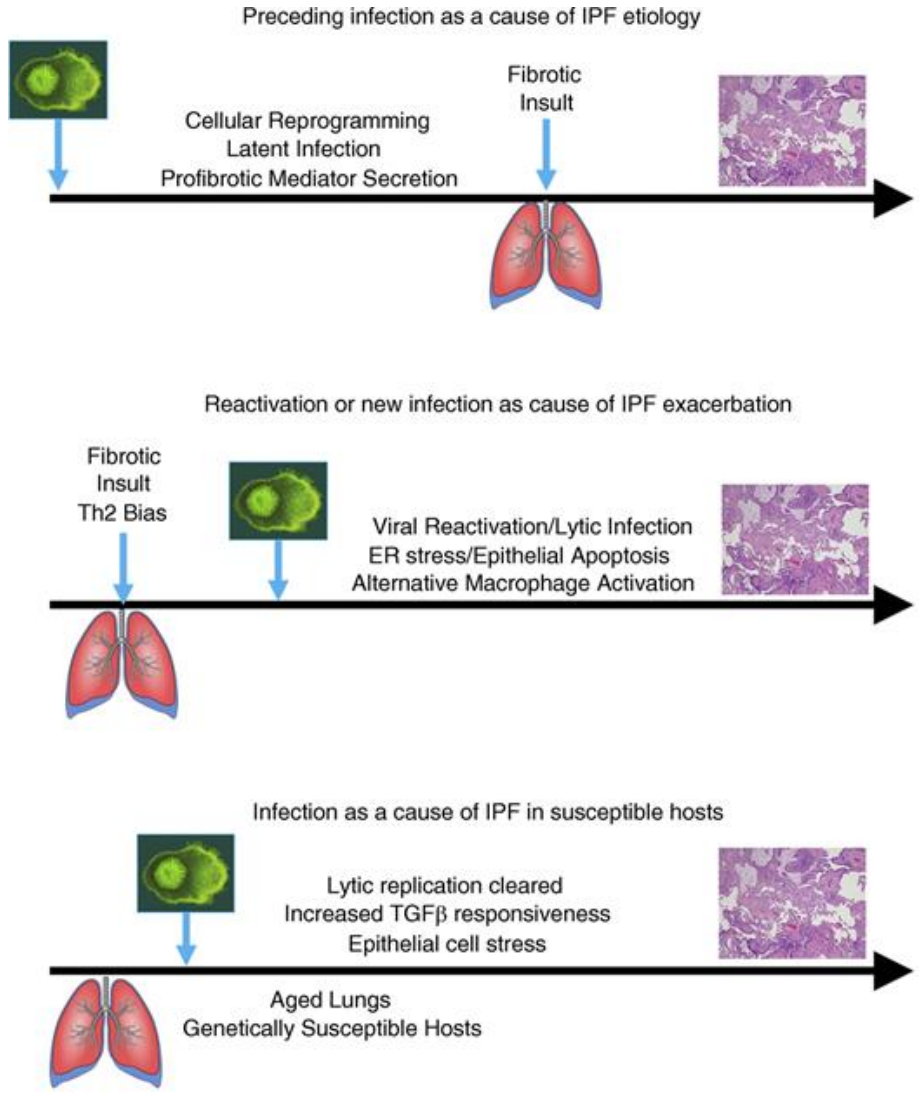
Treatment possibility 2: Antifibrotics



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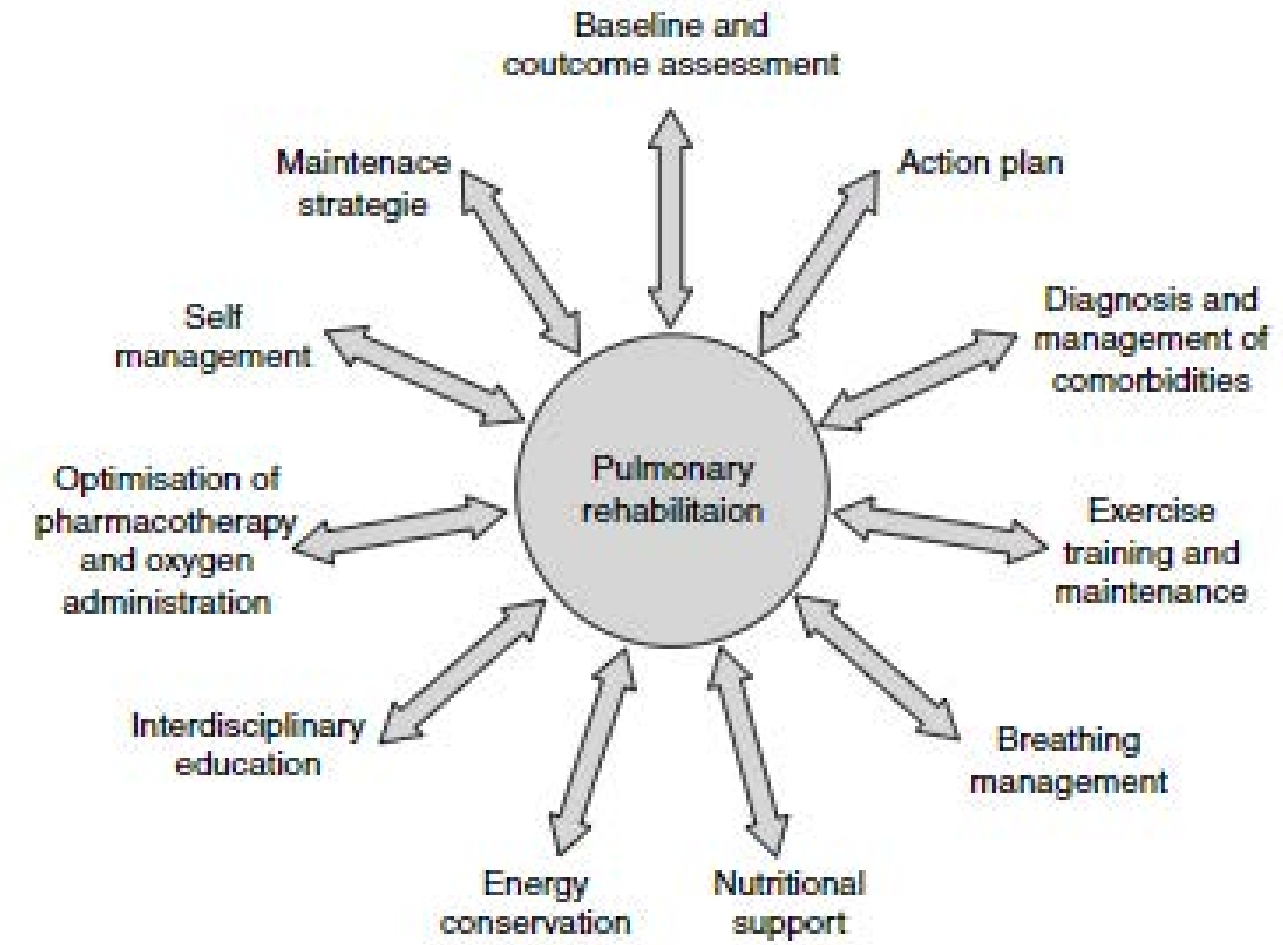
Data Collection Ongoing: Antifibrotics

Trial	Location and Status
Phase-II Randomized Clinical Trial to Evaluate the Effect of Pirfenidone Compared to Placebo in Post-COVID19 Pulmonary Fibrosis	Completed Spain
Pirfenidone vs. Nintedanib for Fibrotic Lung Disease After Coronavirus Disease-19 Pneumonia (PINCER) -	Ongoing since March 2021 India
BIO 300 Oral Suspension in Discharged COVID-19 Patients (1500mg Genistein QD for 12 weeks)	University of Colorado Anschutz Medical Campus Aurora, Colorado NYU Langone Health New York, New York, United States Houston Methodist Research Institute Houston, Texas, United States
Use of Nintedanib in Slowing Lung Fibrosis in Patients With Pulmonary Infiltrates Related to COVID-19	Mount Sinai Beth Israel New York, New York, United States Icahn School of Medicine at Mount Sin

Treatment possibility 3: Pulmonary Rehabilitation



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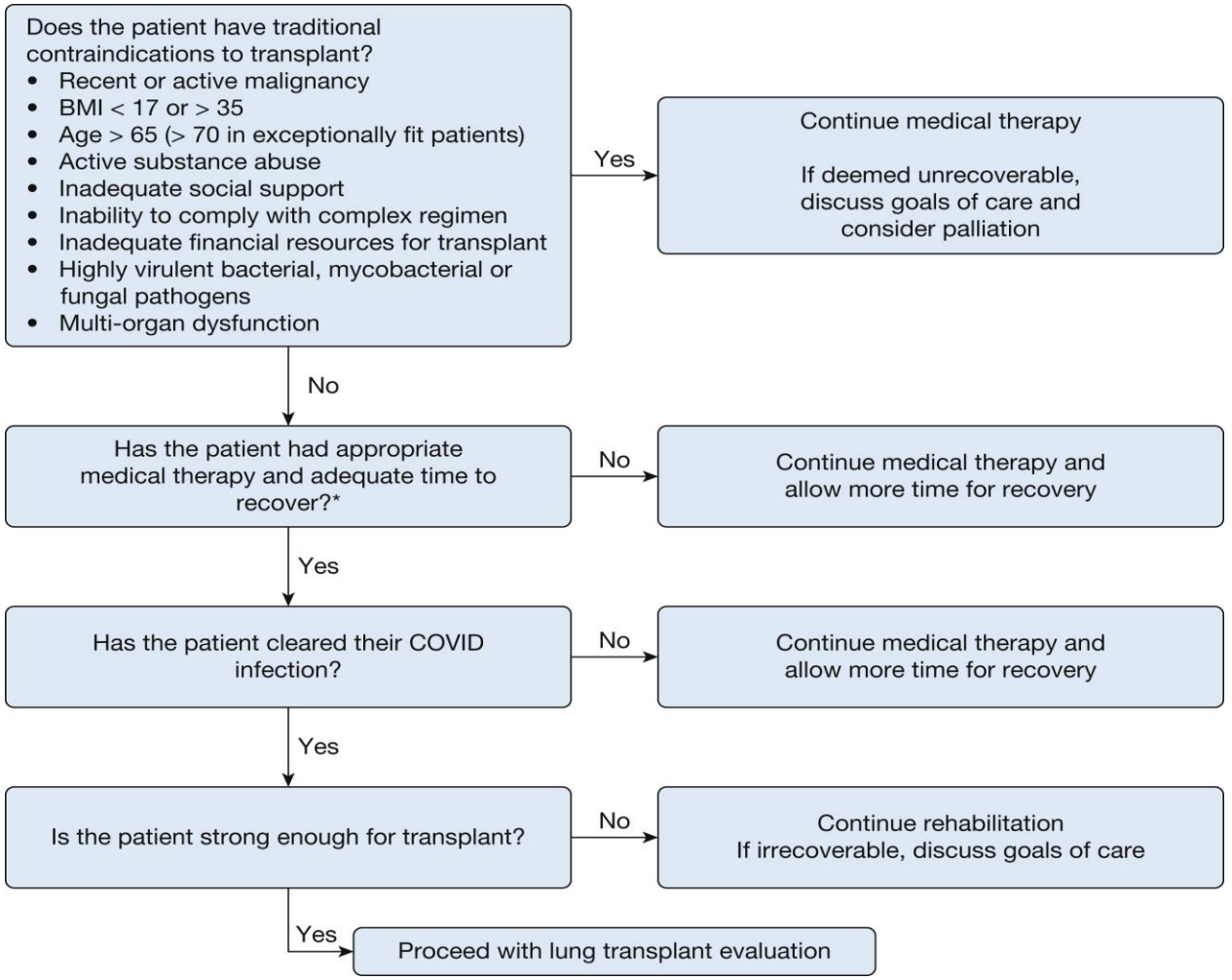
Treatment Possibility 4: Lung Transplantation

Considerations Before Transplantation in Outpatients With Post-COVID Fibrosis
Assess for evidence of preexisting ILD
• History: Symptoms before COVID-19 infection, family history of ILD, connective tissue disease history or signs/symptoms, occupational or other exposures associated with chronic hypersensitivity pneumonitis
• Review available chest imaging from before COVID-19 infection
• Consider connective tissue disease testing
Obtain baseline PFTs, 6MWT, and imaging, and monitor serially
Consider a trial of corticosteroids
Consider anti-fibrotic (pirfenidone or nintedanib) if evidence of progression
Refer for pulmonary rehabilitation
Transplantation is reserved for severe debility failing to improve with time, medical therapy, and rehabilitation or progressive disease

King CS, Mannem H, Kukreja J, Aryal S, Tang D, Singer JP, Bharat A, Behr J, Nathan SD. Lung Transplantation of COVID-19 Patients: How I Do It. Chest. 2021 Aug 19:S0012-3692(21)03668-0. doi: 10.1016/j.chest.2021.08.041. Epub ahead of print. PMID: 34418410; PMCID: PMC8373594

Treatment Possibility 4: Lung Transplantation =Last Resort



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Preliminary Data: Lung Transplantation

- A query of the United Network for Organ Sharing (UNOS) showed that as of April 30,2021, only 78 lung transplants carrying a recipient diagnosis of COVID-19 had been performed in the United States: 5O for COVID ARDS and 28 for COVID Fibrosis

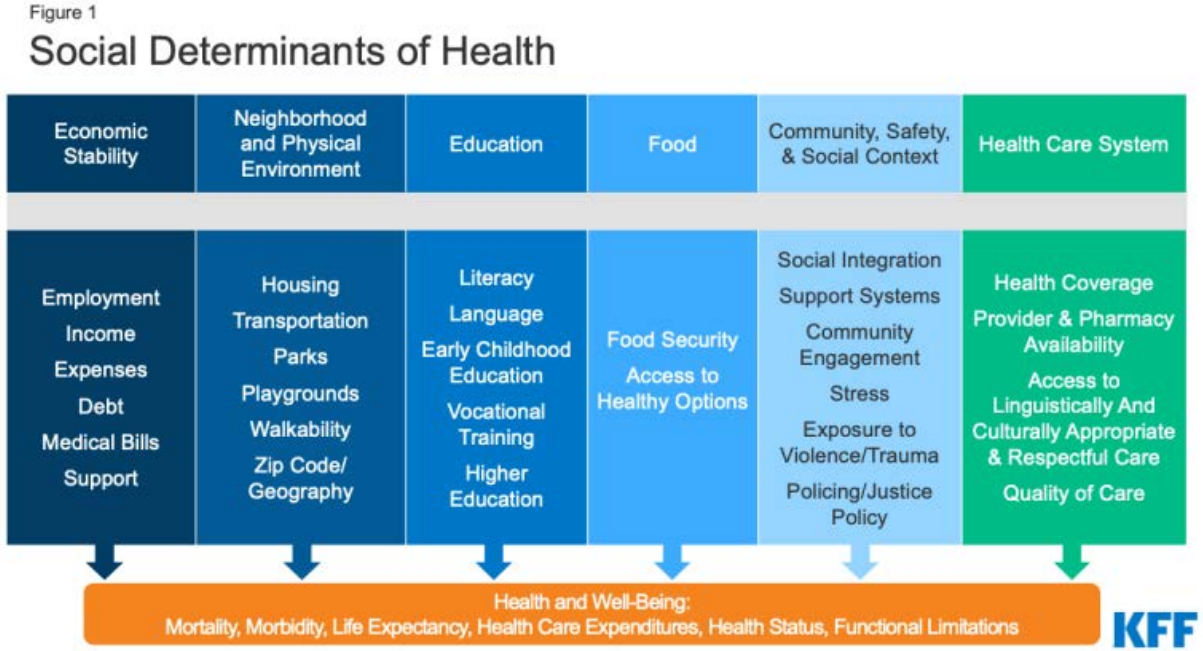
- As of April 23,2021, the Eurotransplant consortium (responsible for organ allocation in Austria, Belgium, Croatia, Germany, Hungary, Luxemburg, the Netherlands, and Slovenia)reported only 21 patients undergoing transplantation for a diagnosis of COVID-19

- Very little data exists on patients post-transplant, however one study of 54 patients transplanted at UT Southwestern demonstrated that significant proportion of COVID-19 survivors suffer persistent allo- graft injury.

King CS, Mannem H, Kukreja J, Aryal S, Tang D, Singer JP, Bharat A, Behr J, Nathan SD. Lung Transplantation of COVID-19 Patients: How I Do It. Chest. 2021 Aug 19:S0012-3692(21)03668-0. doi: 10.1016/j.chest.2021.08.041. Epub ahead of print. PMID: 34418410; PMCID: PMC8373594
Mahan LD, Lill I, Halverson Q, Mohanka MR, Lawrence A, Joerns J, Bollineni S, Kaza V, La Hoz RM, Zhang S, Kershaw CD, Terada LS, Torres F, Banga A. Post-infection pulmonary sequelae after COVID-19 among patients with lung transplantation. Transpl Infect Dis. 2021 Oct 4:e13739. doi: 10.1111/tid.13739. Epub ahead of print. PMID: 34605596

Problem 3: Diagnosis is made difficult with varying risk factors, varying natural history of

- The development of long COVID has been identified with more frequency in patients with higher body mass index (BMI), older age and Black, Asian and Minority ethnic groups
- The post-acute COVID-19 Chinese study demonstrated that women were more likely to experience fatigue and anxiety/depression at 6 months follow-up



Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* **397**, 220–232 (2021).
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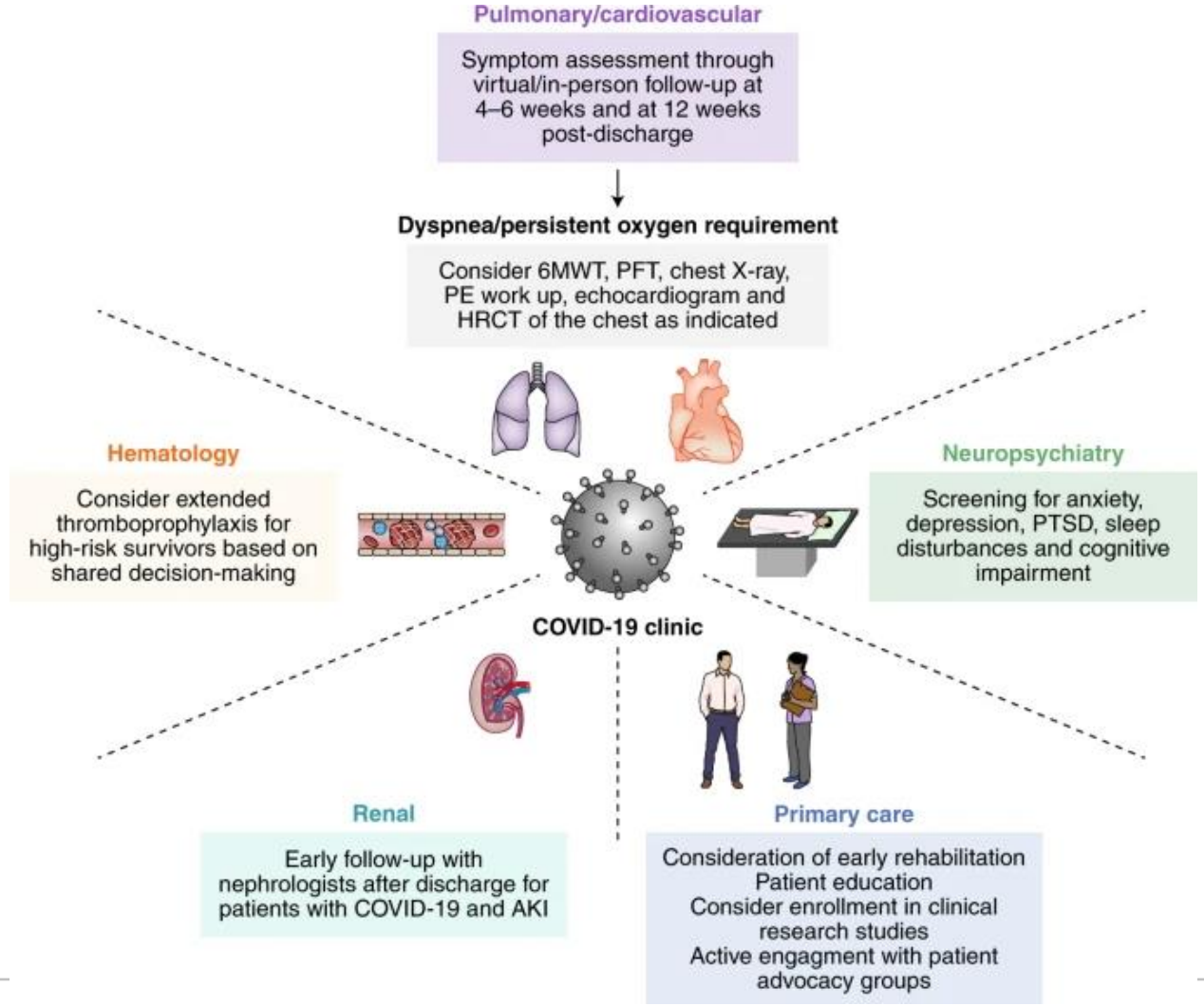
Nalbandian, A., Sehgal, K., Gupta, A. et al. Post-acute COVID-19 syndrome. Nat Med 27, 601–615 (2021). https://doi.org/10.1038/s41591-021-01283-z
Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. *Lancet Respir Med*. 2020;8(7):659-661. doi:10.1016/S2213-2600(20)30234-4
Tracking Social Determinants of Health During the COVID-19 Pandemic Published: Oct 21, 2021 Kaiser Family Foundation

Opportunity 3: Diagnosis is made easier with well coordinated integrated primary and subspecialty care



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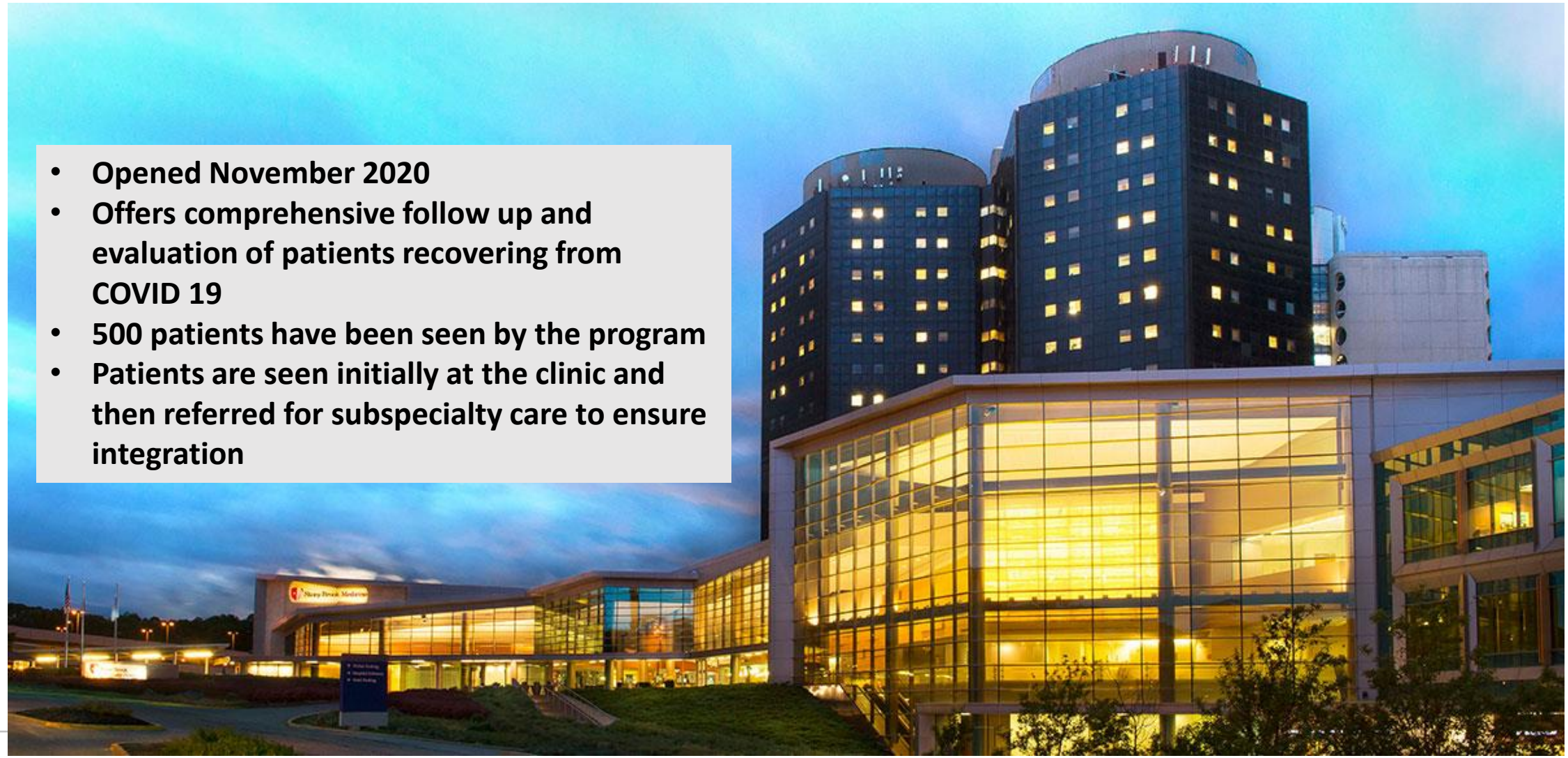
Stony Brook University Hospital Post-COVID Clinic



- Opened November 2020
- Offers comprehensive follow up and evaluation of patients recovering from COVID 19
- 500 patients have been seen by the program
- Patients are seen initially at the clinic and then referred for subspecialty care to ensure integration

Stony Brook University Hospital Post-COVID Clinic

Sritha Rajupet, MD MPH
Family and Preventive Medicine

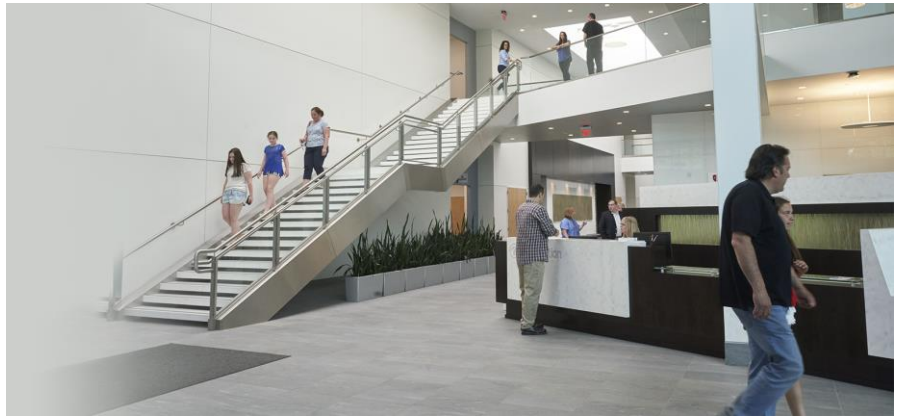
Jenna Palladino PsyD

Specialty Services Offered in the Post-COVID Clinic:

- Cardiology
- Infectious Disease
- Internal Medicine
- Mental Health Services, including Stony Brook Medicine's COVID-19 Support Group
- Nephrology
- Neurology
- Pulmonary
- Vascular Care

Diagnostic Services offered:

- Pulmonary Function Testing
- Cardiopulmonary Exercise Testing
- 6 Minute Walk Testing
- Stress Test Lab
- Echocardiography
- Imaging
- Laboratory Services



How To Make An Appointment

Post COVID-19 Clinic Appointment Request

Stony Brook Medicine Advanced Specialty Care
500 Commack Road, Suite 203
Commack, NY 11725
(631) 638-0597

Please provide the information requested below and we will be in touch to help schedule your appointment. We try our best to respond within 36 business hours. If you are having urgent symptoms, please speak with your physician and go to the nearest emergency room for care.

* Required

1. FIRST NAME *

Enter your First Name exactly as it appears on your license.

Enter your answer

2. LAST NAME *

Enter your Last Name exactly as it appears on your license.

Enter your answer

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