

# Post COVID Syndrome: An Overview and Approach to Management

---

March 30, 2021



# Housekeeping



- You will need to call in to speak on the line; however, it is recommended that you call in even if you're just listening on the line for a better user experience:
  - Conference number: 1-866-814-9555
  - Participant passcode: 723 288 1431
- All phone lines have been muted.
- During the Q&A portion, you may unmute your phone line by pressing #6. You can also use the participant chat to ask questions.
- Today's session recording and slides will be available on the [aidsetc.org](http://aidsetc.org) website as a resource.

# Speakers



**Renslow D. Sherer,  
MD**



**Jameela J. Yusuff,  
MD, MPH, MSHCDL,  
FACP**



**Prathit A. Kulkarni, MD,  
FACP**



**Susan Swindells, MBBS**

# Disclosures

- Dr. Sherer receives research funding from Gilead Sciences, Inc.
- Dr. Swindells reports research grants to her institution from ViiV Healthcare
- Drs. Yusuff and Kulkarni have no conflict of interests to disclose



# Learning Objectives

- Define post COVID syndrome and describe its clinical characteristics
- Review useful strategies for the diagnosis and management of post COVID syndrome

# Post Acute Sequelae of COVID-19

# OUTLINE

- What is Post-Acute Sequelae COVID-19 (PASC)?
- What are the predominant sign/symptoms
- What are the specific end organ disease?
- What are the management strategies?
- What are areas for further research?

# Long COVID = Long Hauler = PASC

As reports of long-term COVID-19 symptoms emerged, the need for scientific research about **long COVID** has intensified.

## Newsweek

'I Got COVID 9 Months Ago and Still Have Symptoms'

## 60 MINUTES

PUZZLING, OFTEN DEBILITATING AFTER-EFFECTS PLAGUING COVID-19 "LONG-HAULERS"

Doctors are still searching for answers to why a portion of people who were diagnosed with COVID-19 are still suffering symptoms months later. Anderson Cooper reports

## SCIENTIFIC AMERICAN

LOCAL / WEATHER KNIGHT

S.F. Millennial was fit and healthy before COVID-19. He's a disabled 'long-hauler' now

Weather Knight | JAN 15, 2021 | UPDATED JAN 15, 2021 4:32 PM

## The New York Times

*For Long-Haulers, Covid-19 Takes a Toll on Mind as Well as Body*

"It makes you depressed, anxious that it's never going to go away."



Coronavirus survivors plagued by long-term ailments

Symptoms include losing sense of smell, dry cough, fever and chronic fatigue



SHORT WAVE

What's It Like To Be A COVID-19 'Long Hauler'

November 9, 2020 - 4:00 AM ET

## San Francisco Chronicle

PUBLIC HEALTH | OPINION

The Problem of 'Long Haul' COVID

More and more patients are dealing with major symptoms that linger for months

By Carolyn Barber on December 29, 2020

## Vox

The many strange long-term symptoms of Covid-19, explained

Long Covid "is a phenomenon that is really quite real and quite extensive," Anthony Fauci said.

By Lois Parshley | Dec 15, 2020, 4:20pm EST



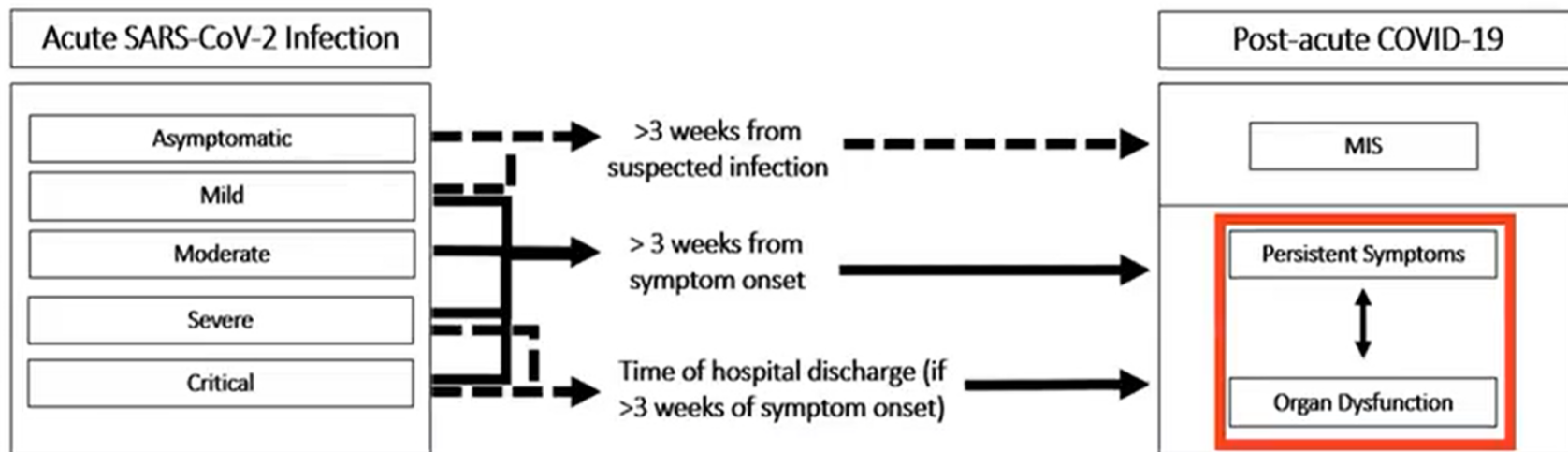
Long Covid: 'I thought I'd get over this no problem'

By Claire Hoyle  
BBC News 10

Often referred to as "Long COVID", these symptoms, which can include fatigue, shortness of breath, "brain fog", sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and **can range from mild to incapacitating**. In some cases, new symptoms arise well after the time of infection or evolve over time. **-NIH**

Preliminary reports indicate some patients may develop a so-called "post-acute COVID-19 syndrome," in which they experience persistent symptoms after recovering from their initial illness. **The syndrome appears to affect those with mild as well as moderate-to-severe disease.** The incidence, natural history and etiology of these symptoms is currently unknown **-CDC**

# Framework for Categorizing PASC



**MIS = Multisystem  
Inflammatory Syndrome**

**There is likely a relationship between organ dysfunction and persistent symptoms that is not yet completely understood.**

Ameta EM et al. OFID. 2020 Oct 21;ofaa509.

# Varying Definitions of When PASC Starts

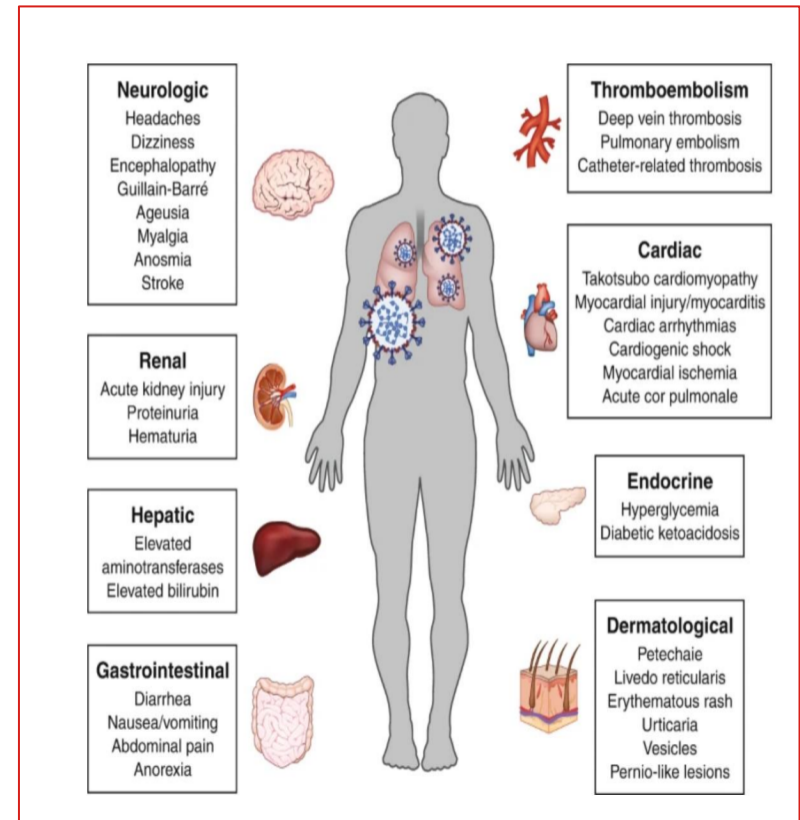
- OFID: Framework of PASC estimated 3 weeks post infection
- CDC JAMA: Proposed Framework of Timeline: suggests 4 weeks post infection
- Guidelines from the UK's National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP).
- Their breakdown is as follows:
  - **Acute COVID-19:** signs and symptoms of COVID-19 for up to 4 weeks.
  - **Ongoing symptomatic COVID-19:** signs and symptoms of COVID-19 from 4 to 12 weeks.
  - **Post-COVID-19 syndrome:** signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis

<https://www.nice.org.uk/guidance/NG188>

Open Forum Infect Dis. 2020 Oct 21;7(12):ofaa509. doi: 10.1093/ofid/ofaa509. PMID: 33403218  
JAMA. 2020 Dec 8;324(22):2251-2252. doi: 10.1001/jama.2020.22717. PMID: 33206133.

# Long-Term Sequelae of COVID-19

- Limited peer reviewed data
- Severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infection long term complications not uncommon
  - Depression, anxiety, post-traumatic stress disorder (PTSD) and post-intensive care syndrome (PICS)
- Entry receptor angiotensin-converting enzyme 2 (ACE2) expressed in extrapulmonary tissue



# Symptom Persistence



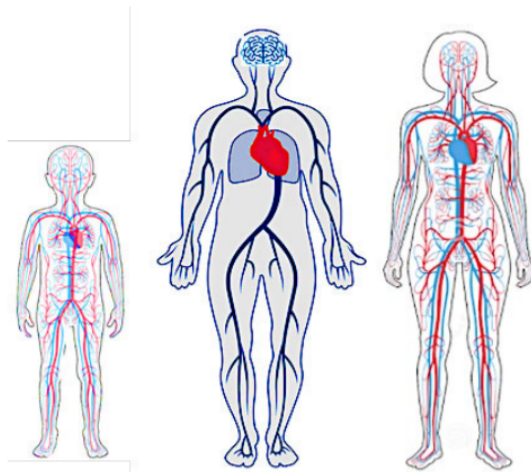
# Symptom Persistence Among Inpatients

## COVID-19: Persistent Symptoms in Hospitalized Patient *A Multi-Organ, Multi-System Clinical Presentation*

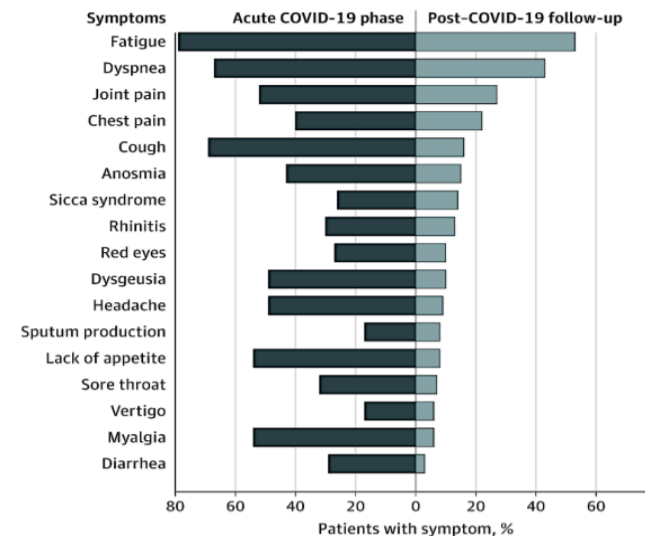
120 patients (mean = 111 days post admission)

### Persistent symptoms

- Fatigue 55%
- Difficulty breathing 42%
- Memory loss 34%
- Sleep disorder 32%
- Attention disorder 27%
- Significant hair loss 20%
- Cough 17%
- Loss of smell 13%
- Chest pain 11%
- Loss of taste 11%



143 patients (mean 60 days post onset)



Garrigues et al. Infect. 2020 Aug 25:S0163-4453  
<https://doi.org/10.1016/j.jinf.2020.08.029>

Carifi, et. al. JAMA. 2020;324(6):603-605.  
 doi:10.1001/jama.2020.12603

# Symptom Predominance Among Outpatients



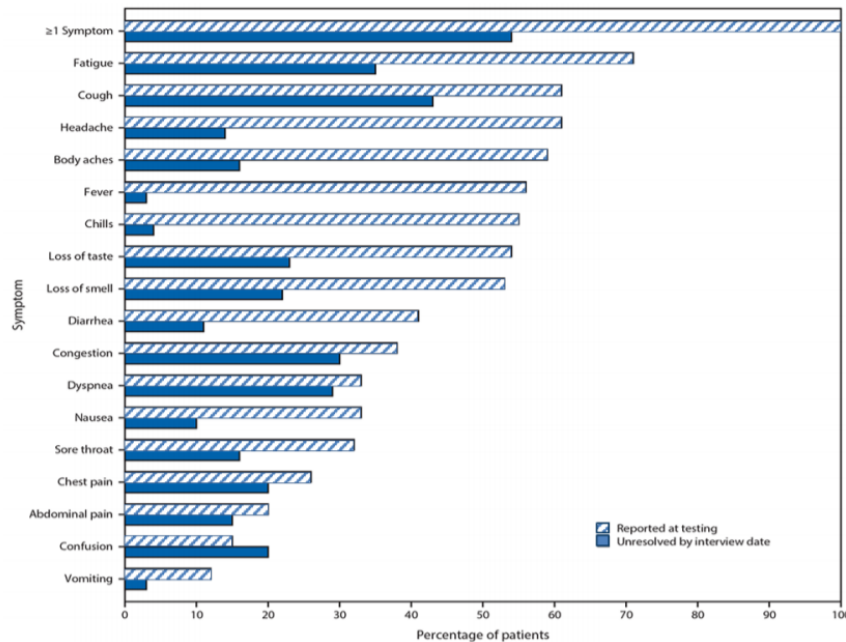
Centers for Disease Control and Prevention  
CDC 24/7: Saving Lives, Protecting People™

July 31, 2020

Morbidity and Mortality Weekly Report (MMWR)

## Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

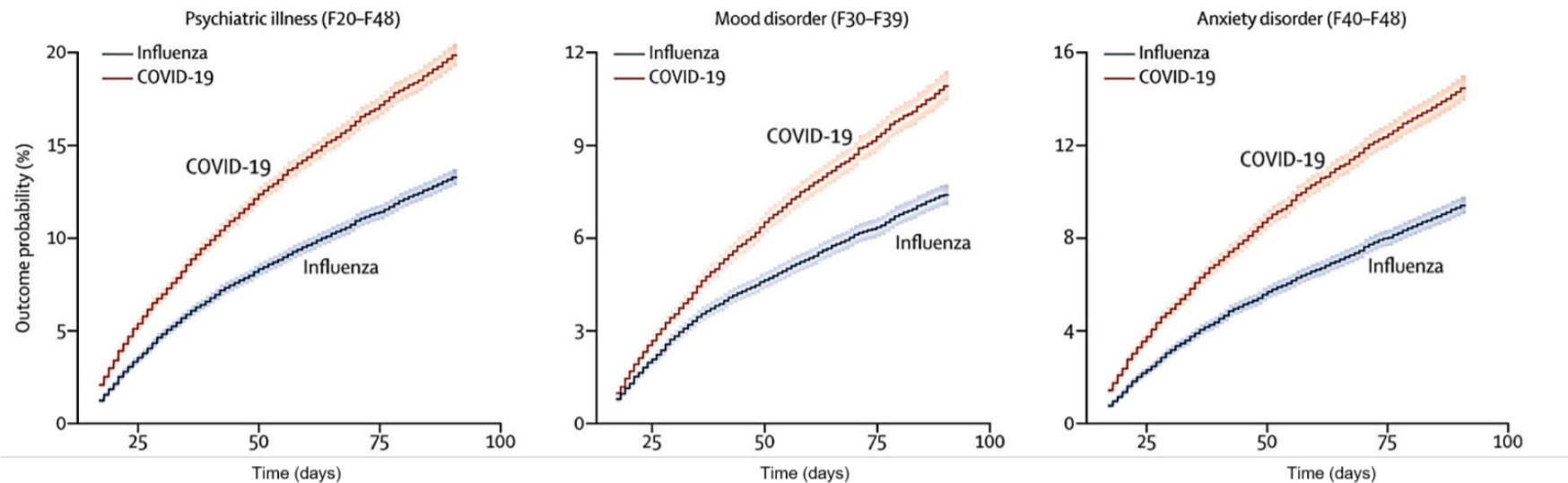
MW Tenforde, LR Feldstein et al. for the IVY Network Investigators and CDC COVID-19 Response Team



Among symptomatic non hospitalized patients with positive test for SARS-CoV-2, 35% not returned to baseline health 2-3 weeks after testing

- Older age and comorbidities associated with lack of return to baseline health
- 19% of young adults (18-34) with no comorbidities had not returned to baseline health
- In contrast 90% of influenza outpatients recover within 2 weeks

## New diagnoses of anxiety, insomnia, dementia, and mood disorders, as well as psychiatric disorders in general, were increased after COVID-19 illness



[www.thelancet.com/psychiatry](https://www.thelancet.com/psychiatry) Published online November 9, 2020 [https://doi.org/10.1016/S2215-0366\(20\)30462-4](https://doi.org/10.1016/S2215-0366(20)30462-4)

10

# ORGAN DYSFUNCTION

# NEUROLOGIC INVOLVEMENT

# Neurologic Sequelae

## ■ Acute Manifestations

- Headache, vertigo, weakness, anosmia, ageusia
- Encephalopathy, seizures, strokes,
- Guillain Barre

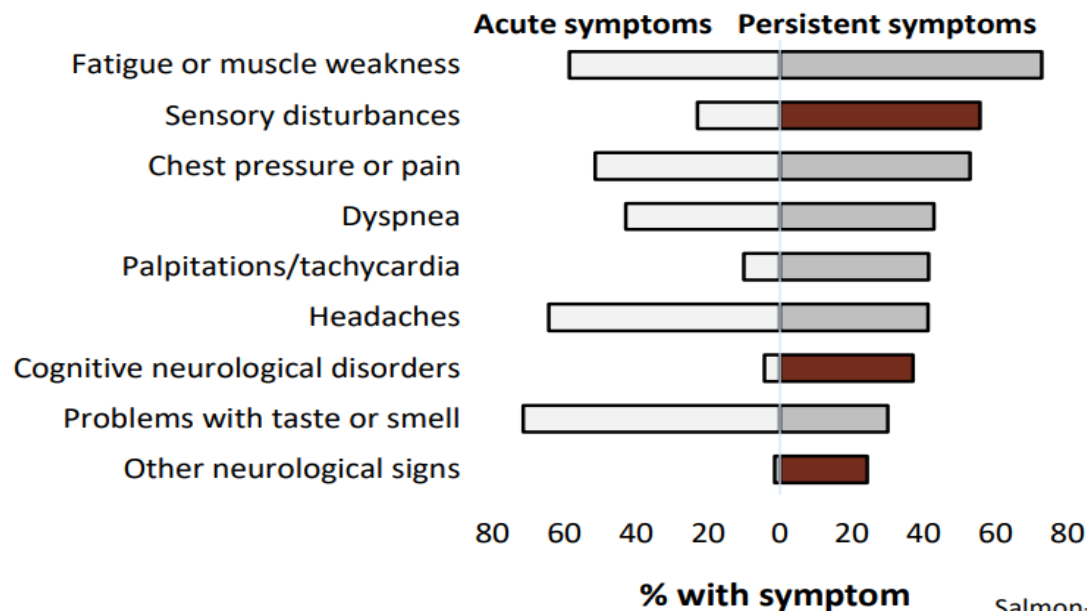
## ■ Post-Acute Manifestations

- Major Mood swings-depression/anxiety
- “Brain Fog”
- Dysautonomia
- Paresthesias
- Headaches

# Long Term Neurologic Symptoms

**More than one quarter of patients developed new neurological symptoms** after their acute COVID-19 illness.

COVID-19 symptoms among 70 non-hospitalized patients, France



Salmon-Ceron et al., J Infect. 2020



# Possible Neurologic Workup for Symptoms

- History/Physical Exam:
  - Age, comorbidities, course of COVID, other screening for PTSD, depression and psychiatric screening
- Lab:
  - Standard labs, HIV, HgbA1c, B12, TSH, Rheum w/u
- Imaging:
  - Consider MRI, MRA
- Other testing:
  - EMG, EEG, Orthostatic, tilt table



# Possible Treatment Modalities

- **Brain fog:** – No specific treatment – Address any abnormalities in bloodwork – Address contributing factors – If attention is major issue: Atomoxetine, dextroamphetamine/amphetamine, methylphenidate, modafinil
- **Dysautonomia:** – Hydration, increase salt intake, compression stockings – Meditation, breathwork – Postural Orthostatic Tachycardia Syndrome (POTS): consider adding in midodrine or fludrocortisone – Hyperadrenergic POTS: betablocker
- **Small fiber neuropathy:** – Address any abnormalities in bloodwork – Symptomatic treatment of paresthesias: gabapentin, pregabalin, tricyclics, duloxetine – Dysautonomia as above
- **Fatigue:** Pacing of exercise: low-impact, short duration exercise with gradual increase. Do not push to recondition quickly.
- **Sleep:** – Sleep hygiene – Assess for possible sleep apnea – Sleep aids: melatonin, mirtazapine, gabapentin or amitriptyline (if paresthesias or headaches also present)
- **Mental Health:** Depression, anxiety and PTSD can affect cognition; Anti-depressants like duloxetine or venlafaxine may be beneficial in also treating paresthesias and/or headaches

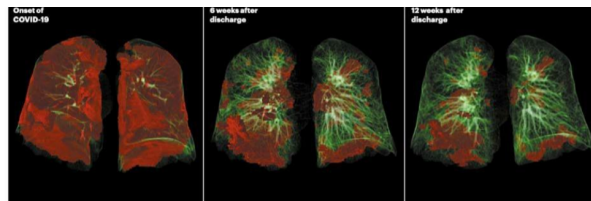
# PULMONARY INVOLVEMENT

# Pulmonary

- Acute Manifestations
  - Pneumonia
  - Acute respiratory distress syndrome (ARDS)
  - Hypoxic respiratory failure
- Post-Acute Manifestations
  - Signs and symptoms of chronic fibrosis and restrictive lung disease

# Pulmonary Sequelae

- In 55 COVID survivors symptoms of restrictive lung disease common among those hospitalized
  - 30 days: 53% DLCO
  - 3 months: 25% DLCO
  - 3 months: 71% evidence of interstitial thickening



Lung scans from a 50-year-old show that damage from COVID-19 (red) can improve with time — but many patients have lasting symptoms.

Zhao YM et al Eclinical Medicine 2020;25:100463

- 150 patients with noncritical COVID were followed 2 months found:
  - 30 days: 36.7% with dyspnea
  - 60 days: 30% with dyspnea

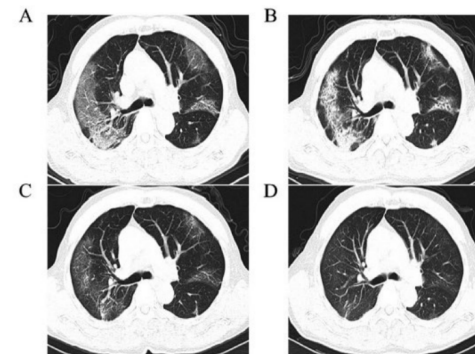
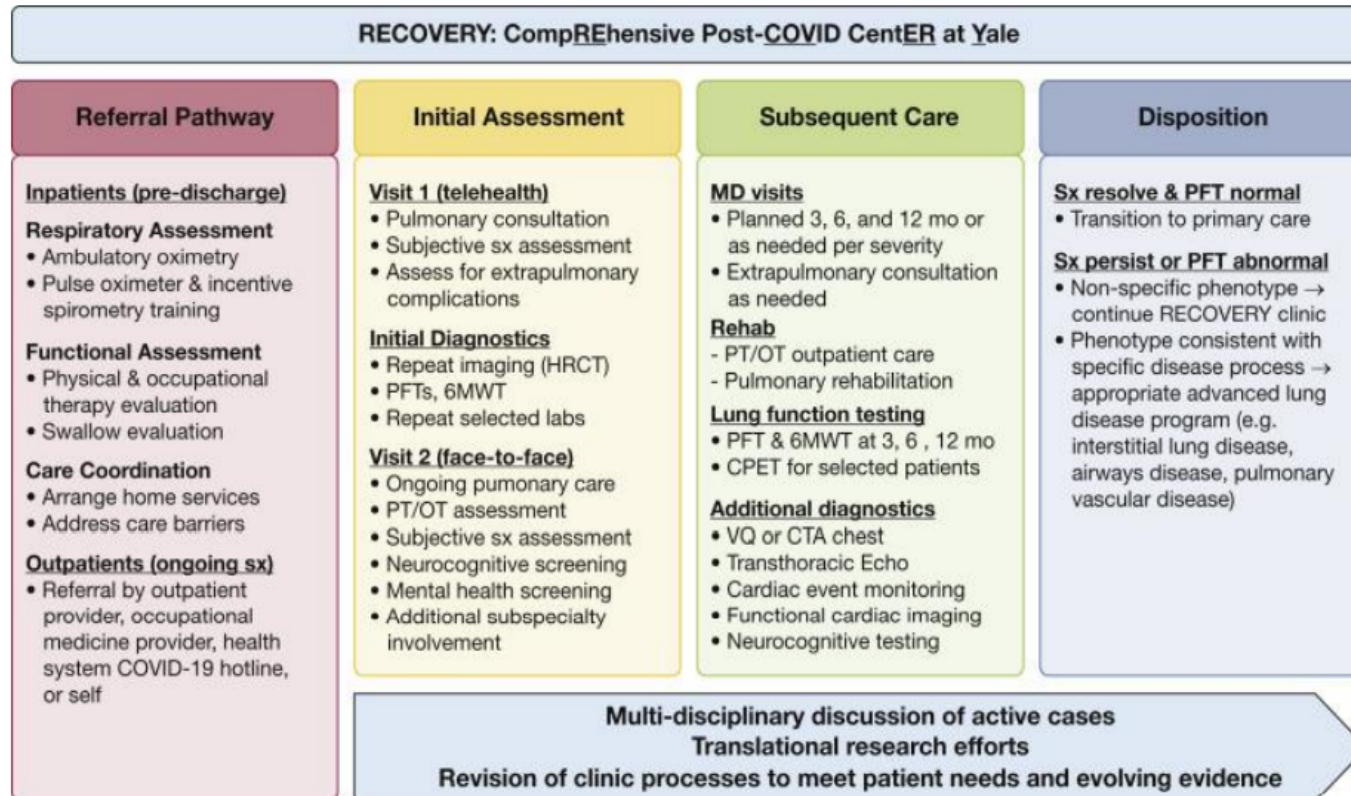


Fig. 2. Follow-up thin-section CT imaging of 63-year-old man with confirmed COVID.

Huang Y, Respir Res, 2020;21(1):163

# Our initial clinical model: Post COVID Clinic Pathway at Yale



# CARDIAC INVOLVEMENT

# Cardiovascular

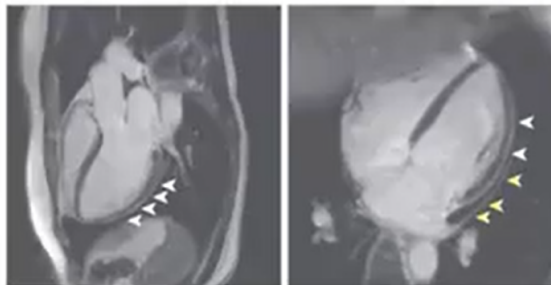
- Acute Manifestations
  - Cardiac injury
  - Myocarditis
  - Arrhythmias
  - Cardiogenic shock
- Post-acute manifestations
  - Myocarditis
  - Arrhythmia
  - Cardiomyopathy

# MRI Outcomes in Patients Recovered

JAMA Cardiology | Original Investigation

Outcomes of Cardiovascular Magnetic Resonance Imaging  
in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

- German study, n=100
- Cardiac MRI done in median 71 days after COVID-19 diagnosis
- Cardiac involvement in 78%
- Ongoing myocardial inflammation in 60%
- Presence of chronic comorbidities, duration and severity of acute COVID-19 time since original diagnosis did not correlate with findings



**Non-random sample likely biased  
toward cardiac findings.**

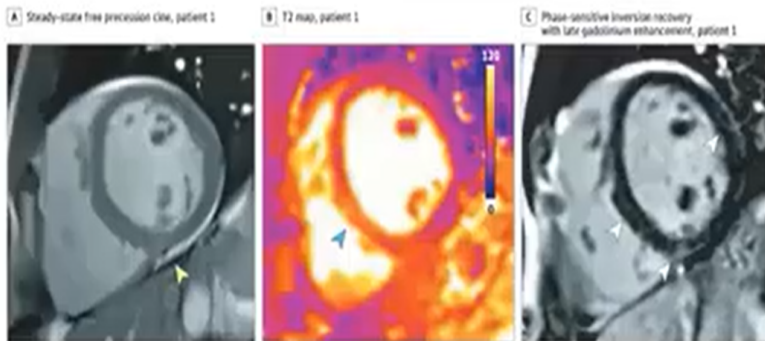


# MRI Findings in Athletes

## RESEARCH LETTER

### Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection

Figure: Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From Coronavirus Disease 2019 Infection



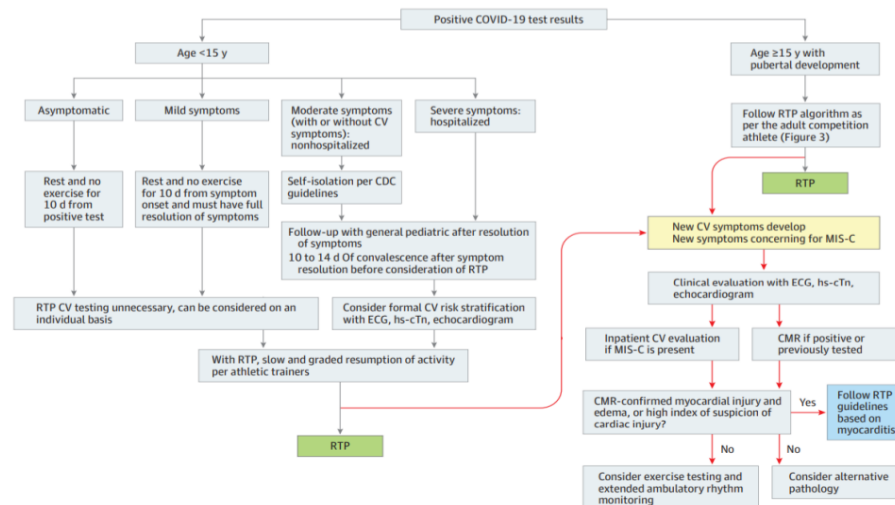
- 26 competitive college athletes diagnosed with COVID-19
- None were hospitalized
- Majority had no symptoms
- 12 (46%) had evidence of myocarditis or prior myocardial injury by cardiac MRI (12-53 days)

# Cardiac Algorithms for Athletes



## Coronavirus Disease 2019 and the Athletic Heart Emerging Perspectives on Pathology, Risks, and Return to Play

Jonathan H. Kim, MD, MSc; Benjamin D. Levine, MD; Dermot Phelan, MD, PhD; Michael S. Emery, MD, MS;  
Mathew W. Martinez, MD; Eugene H. Chung, MD, MSc; Paul D. Thompson, MD; Aaron L. Baggish, MD



## Return to Play for Athletes After Coronavirus Disease 2019 Infection— Making High-Stakes Recommendations as Data Evolve

James E. Udelson, MD; Michael A. Curtis, MEd, CSCS; Ethan J. Rowin, MD

- Complex algorithms published for high school athletes, adult engaged in recreational sports, and professional athletes
- Slow escalation of activity recommended for those with mild COVID and no CV symptoms
- Aggressive work-up (ECG, troponins, echocardiogram) for those with CV symptoms (particularly syncope), progressing to CMR as needed

# RECOVERY AND FOLLOW-UP

# Other Aspects of Recovery

- Provide multidisciplinary clinics
  - Respiratory, Cardiology and Neurology specialty care
  - Rehabilitation requirements
  - Case management support for housing and food
- Listen to our patients
  - Mental health care for anxiety and depression
    - Referrals for counseling and peer support
  - Self management for disease monitoring
- Public Health Messaging for young people to avoid infection—it's not all about COVID Mortality

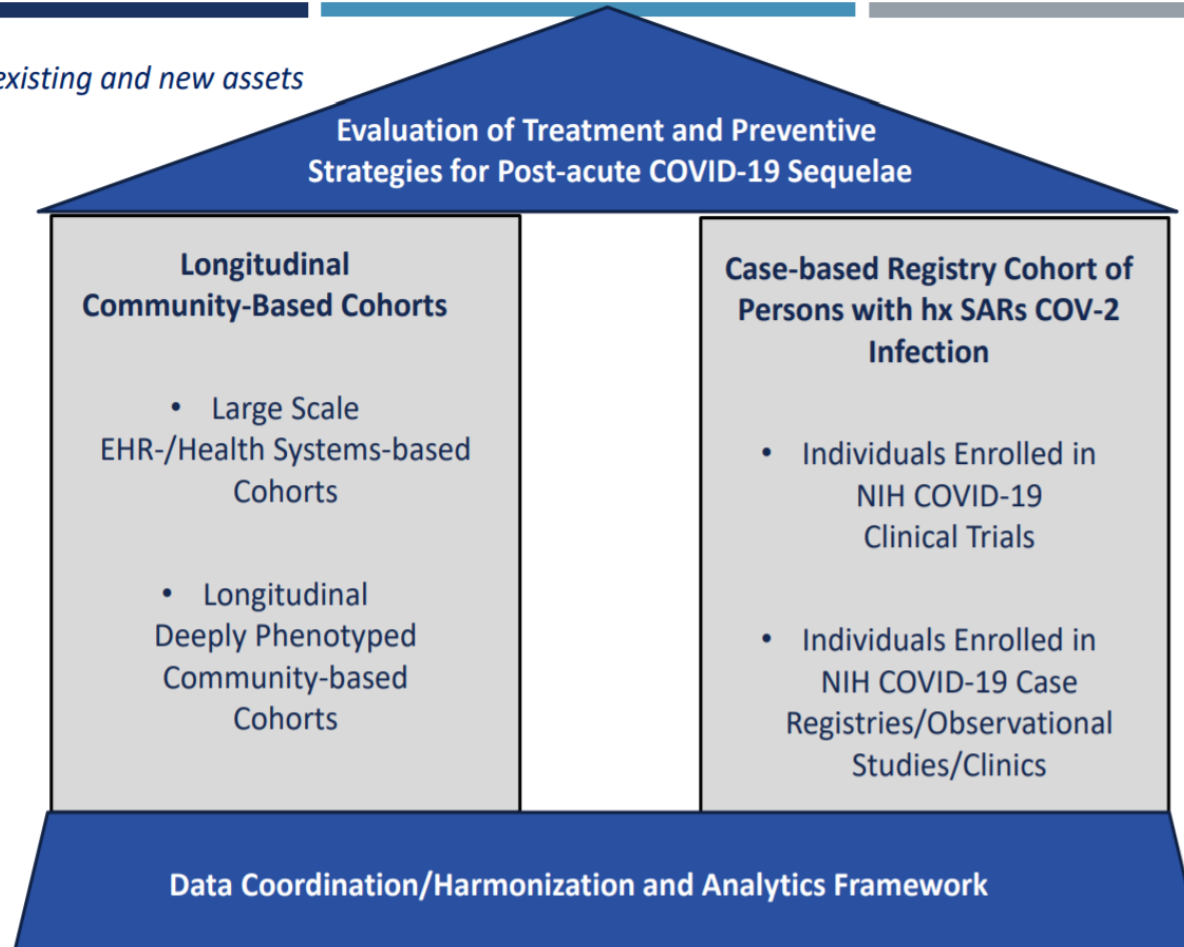
# Recovery...what we still don't know..

- What is the spectrum of clinical “recovery” from COVID-19?
- What interventions might enhance or hasten recovery?
- What is the spectrum of tissue injury due to COVID-19 infection?
- Will unabated symptoms lead to chronic illness in a subset of people?
- Will COVID-19 predispose to other disease in the future?

# FUTURE STUDIES

## NIH Clinical Research Strategy to Understand and Treat Post-acute Sequelae of COVID-19

*Note: Includes existing and new assets*



21

# Resources

- **CDC webpages on PASC:**

- **For the general public:**

<https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html>

- **For clinicians:**

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html>

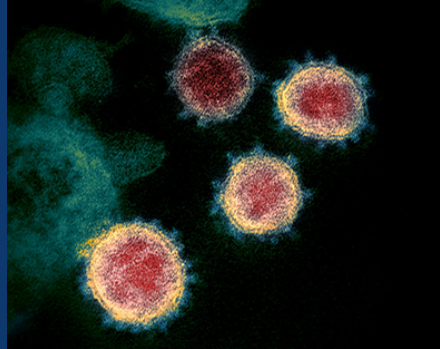
[Webinar January 28, 2021 - Treating Long COVID: Clinician Experience with Post-Acute COVID-19 Care \(cdc.gov\)](#)

- **NIH Workshop on PASC:**

Day 1: <https://videocast.nih.gov/watch=38878>

Day 2: <https://videocast.nih.gov/watch=38879>





# Post COVID Syndromes: Cases

# Case 1

Mario R, aged 22, and his brother live in Chicago. Their father worked in meat packing plant, and he became ill with fever and shortness of breath (SOB) in April, 2020

- Found to be COVID+, hospitalized & died in 2 weeks

Mario and his brother both had anosmia. His brother also had a URI and tested SARS-CoV-2 positive in April, 2020; Mario tested negative, and had no repeat testing, no other symptoms

- Mario's brother recovered fully; 2 cousins in the same building also tested positive, and had no symptoms

Mario developed SOB, fatigue, and joint pain after 3 weeks

- Increasing fatigue, post-exertional exhaustion for 3 months that prevented him from working and attending classes
- Noticed increasing lack of concentration, HA from June – Sept
- Improved but 'still not right' as of Oct, 2020, 6 months later



# Case 1: Questions

## CASE SUMMARY:

22 yo man w/ likely false negative PCR

Initial anosmia only

Post COVID Syndrome with Chronic fatigue, arthralgia, post-exertional exhaustion, HA, & poor concentration x 6 mos

Does Mario require a positive Ag test for the diagnosis of Post COVID Syndrome?

- Is a + SARS-2 Ab test needed?

What is the pathogenesis of this form of post-COVID syndrome?

What medical evaluation should be conducted?

- Differential diagnosis
- Role of PFTs; exercise testing; OT/PT; CT/MRI

What are the options for treatment and management?

What to tell Mario re: prognosis?



## Case 2

Jane P., a 79-year-old ambulatory African-American female presenting to the ED 11/30/20 with 3 days of cough & dyspnea.

- Dry cough and shortness of breath 3 days PTA
  - Symptoms have worsened
- Abdominal pain and decreased appetite for the past 1 week, has been able to tolerate fluids
  - Abdominal pain is intermittent, non-radiating and localized around the periumbilical region

Contact w/ son who is CTA bus driver, currently at UCM w/ SARS-CoV-2



## Case 2

PMHx: Colon CA 1987, HTN, DM, Obesity

On multiple meds

PE: BP 158/114, Pulse 97, RR 24

T 37.5c, SpO2 99% on RA, alert, in NAD,  
exam unremarkable

CXR: no infiltrates



# Initial Labs

## CBC

WBC	8.0
Hgb	12.8
Plt	165
Neutrophils	72
Lymphocytes	18
Monocytes	10
Eosinophils	0
Basophils	0
Immature Grans.	0.1

## Cardiac Markers

hsTrop	17 -> 19 -> 21 (Ref. <14)
proBNP	442 (Ref. <450)

## CMP

Na	131
K	4.2
Cl	94
CO2	23
BUN	14
Cr	1.4
Gluc	261
Ca	8.6
Total protein	7.4
Albumin	3.9
Tbili	0.3
Bili, conj	<0.1
Bili, unconj	-
Alk Phos	96
AST	35
ALT	30

HgbA1c	10.7
--------	------

## Inflammatory Markers

Fibrinogen	433 (Ref. 180-409)
D Dimer	0.6 (Ref. <0.40)
Ferritin	549 (Ref. 10-220)
ESR	56 (Ref. 1-53)
CRP	85 (Ref. <5)
LDH	312 (Ref. 116-245)
CK	254 (Ref. 9-185)

## Infectious Disease

Blood Cx	Negative
MRSA Screen	Negative
HIV Ab/Ag	Non-reactive
Legionella Urine Ag	Negative
S. pneumo Ag	Negative
RVP	Negative
C. dif PCR	Negative

<b>SARS-COV-2</b>	<b>POSITIVE on 3/29/20</b>
-------------------	----------------------------

Influenza  
A/B

Negative



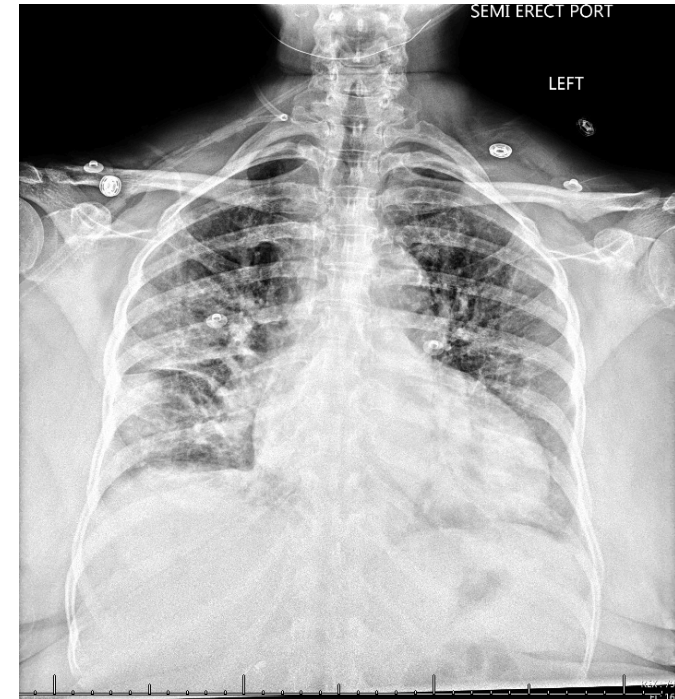
# Initial Assessment & Plan

1. Viral pneumonia due to SARS-CoV2
  - Oxygen support as needed
  - Remdesivir, dexamethasone held due to NL CXR, no O2 requirement
  - Antibiotics held, given afebrile, NL CXR, neg strep/legionella
  - Abdominal pain: Likely related to viral infection
2. Prophylaxis: Started prophylactic dose of LMW Heparin
3. Admitted to COVID unit



# Hospital Course: Day 2

- Interval history
  - Spiked a **fever of 39.5 C** overnight
  - WBC ct 14.1 (from 8.9 on HD 2)
  - Na<sup>+</sup> 128, creat 3.4
  - Increasing O<sub>2</sub> needs: **4 L NC -> 40L HFNC**
  - Started **remdesivir** 200 mg IV for 5 days
  - Started **dexamethasone** 6 mg po x 10d
  - Started cefdinir & azithromycin
- Assessment/Plan
  - Hypoxic respiratory failure: Hold intubation for now
  - Hyponatremia: Fluid restrict + high-dose furosemide
  - Nephrology consult: Confirmed ATN w/ urine sediment
  - ***Transferred to COVID ICU***



**HD 2:** Increase in hazy mid and lower lung opacities consistent with atypical infection given history.



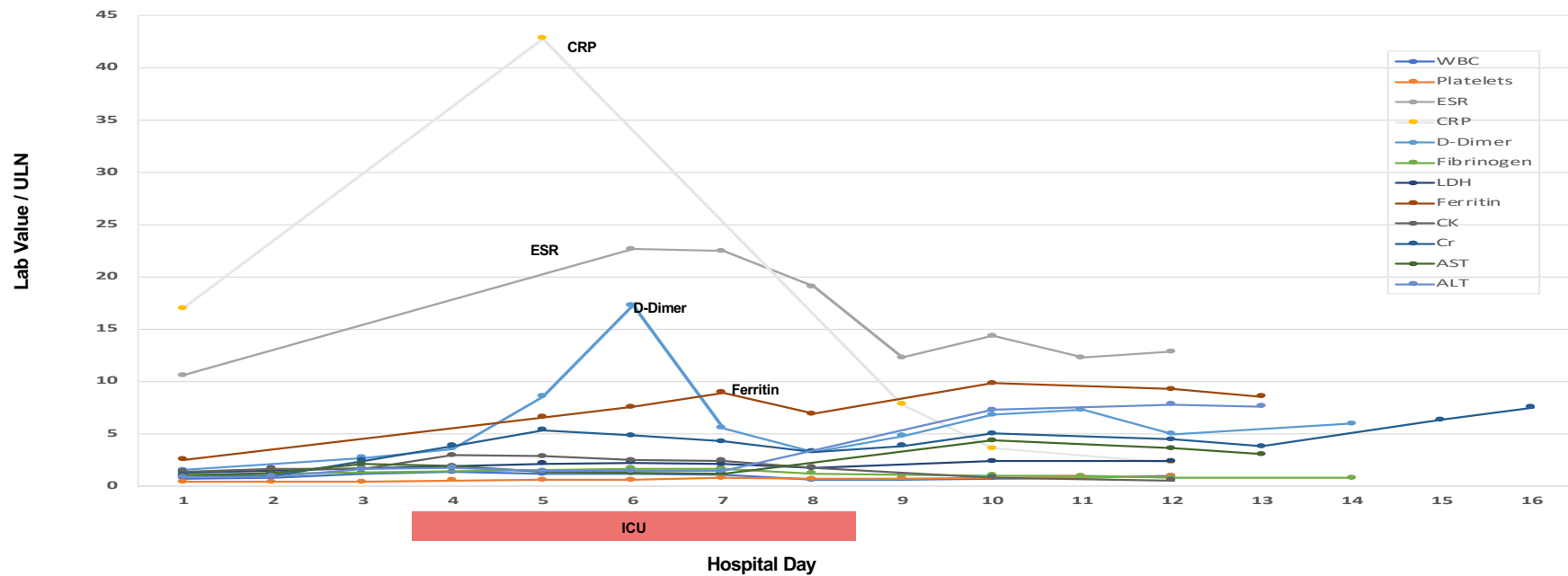


# Hospital Course: Days 4 – 5

- Interval history
  - Hypothermia, AMS, agitation
  - 40L HFNC, 80% FiO<sub>2</sub>
  - D-DIMER 6.9, CRP 125, creat 5.2
  - Doppler shows bilat DVT
- Assessment/Plan
  - Poss SIADH; Continuous dialysis (CVVHD) begin
  - Hypoxic respiratory failure not improved
  - Cytokine release syndrome likely
  - Tocilizumab 400 mg IV given
  - Full anti-coagulation begun



Select Laboratory Values Trended Over Hospital Admission



Hospital Day	One	Two	Three	Four	Five	Six	Seven	Eight	Nine	Ten	Eleven	Twelve	Thirteen	Fourteen	Fifteen	Sixteen
Location	ED	Floor	Floor	ICU	ICU	ICU	ICU	ICU	Floor	Floor	Floor	Floor	Floor	Floor	Floor	Floor/Home
Respiratory Support	2 L NC	4 L NC	5 L NC	15 L NRB	55 L HFNC 60% FIO2	40 L HFNC 80% FIO2	40 L HFNC 40% FIO2	5 L NC	2 L NC	1 L NC	2 L NC	2 L NC	1 L NC	1 L NC	1 L NC	1 L NC
Fever	afebrile	febrile (39.5 C)	afebrile	afebrile	hypothermic (34.3 C)	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile	afebrile
Dialysis					Start CVVHD	Transitioned to iHD										
HCQ																
Lopinavir/Ritonavir																
Tocilizumab																
Other Events			AKI	Confirmed ATN		Intermittent AMS	AMS resolved									



# Hospital Course: Days 6 -10

- Interval history
  - Clinically improving, mentation clear
  - Respiratory req: 2 L NC
  - New transaminitis
- Labs
  - **AST: 160**
  - **ALT: 255**
  - ESR: 76
  - CRP: 18
  - D-dimer: 2.71
  - Ferritin: **2162**
- Assessment/Plan
  - **RUQ ultrasound:** Likely liver pathology – fatty liver - with clear biliary tree
  - Discharge home on 2L O2; **out pt dialysis**



# Case 2: Questions

## CASE SUMMARY:

79 yo w/ severe illness:

Pneumonia, respiratory failure, AKI -> CKD and dialysis, DVTs, high troponins, transaminitis

Issues at discharge:

- HTN, DM, obesity
- Post ARDS pulm. fibrosis
- CKD & dialysis
- DVT & anticoagulation
- F/u liver enzymes
- Post AMS, mental health

- Is Jane's post COVID syndrome the same as case #1?
  - End organ damage vs. immunologic mediation? Both?
- What is the pathogenesis of this form of post COVID syndrome? Was tocilizumab useful in this patient?
- What *additional* medical evaluation should be conducted?
  - Differential diagnoses? Repeat SARS-2 Ag or Ab tests useful?
  - What cardiac evaluation should follow elevated troponins?
  - Role of PFTs and exercise testing?
  - Is CKD reversible?
  - Expected duration of anticoagulation?
  - Does transient AMS require follow up diagnostic evaluation?
- What are the options for treatment and management?
  - Role of rehab, OT/PT, mental health support?
- What to tell Jane re: prognosis?



# Summary

- Post COVID syndrome has been recognized as an important clinical entity during the COVID-19 pandemic
- Currently no universally accepted or agreed upon definition or criteria
- Can be thought of as including persistent symptomatology and/or persistent organ dysfunction
- Future work will aim to clarify the specifics of the syndrome further, as well as underlying pathophysiology and evidence-based management approaches

# Speaker Contact Information

Renslow Sherer, MD

[rsherer@bsd.uchicago.edu](mailto:rsherer@bsd.uchicago.edu)

Jameela J. Yusuff, MD, MPH, MSHCDL, FACP

[Jameela.Yusuff@downstate.edu](mailto:Jameela.Yusuff@downstate.edu)

Prathit A. Kulkarni, MD, FACP

[Prathit.Kulkarni2@bcm.edu](mailto:Prathit.Kulkarni2@bcm.edu)

Susan Swindells, MBBS

[sswindells@unmc.edu](mailto:sswindells@unmc.edu)

<https://aidsetc.org/resource/hiv-sars-cov-2-webinar-series>