

An Update on Post Acute Sequelae from SARS-CoV- 2 Infection (PASC)

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Disclosures

- None in relation to PASC
- PI or Sub-I on COVID clinical trials with the following company
 - Pfizer vaccine trial
 - J and J vaccine trial
 - Gilead
 - Pleurostem
 - Regeneron

Outline

- Definition
- What are the symptoms of PASC?
- Who gets PASC after acute COVID?
- Why does this happen?
- Work-up
- Treatment
- Rehabilitation
- Rehospitalization
- Likelihood of recovery
- Return to work

Definition and Naming of post COVID symptoms

What's in a name?

- Long haul CoVID
- COVID long Haulers
- Continued CoVID
- Post CoVID
- Post-CoVID syndrome
- Post-acute CoVID syndrome
- Post Acute Sequelae of SARS-CoV-2 Infection (PASC)

The variability in definition

Table 1.



Proposed descriptions of long COVID.

Reference	Terms	Description
[4]	Long COVID	Long-term COVID-19 illness that is cyclical, progressive, and multiphasic.
[5,6,7]	Long-hauler COVID-19 Long-COVID Chronic COVID syndrome	Multi-organ symptoms that persist for months after acute COVID-19.
[8]	Long-haul COVID Long-tail COVID	Symptoms lasting for > 100 days.
[9,10]	Long COVID	Symptoms lasting for > 2 months.
[11,12,13]	Late sequelae of SARS-CoV-2 infection Long-haulers Long-COVID	Symptoms lasting for > 4 weeks after the initial infection or diagnosis.
[14]	Post-acute COVID-19 syndrome	Symptoms lasting for > 4 weeks after the first symptom onset.
[15]	Acute post-COVID symptoms Long post-COVID symptoms Persistent post-COVID symptoms	Symptoms lasting for 5-12 weeks. Symptoms lasting for 12-24 weeks. Symptoms lasting for > 24 weeks.
[16, 17,7]	Post-acute COVID-19 On-going symptomatic COVID-19 Chronic COVID-19 Long COVID Post-COVID-19 syndrome	Symptoms lasting for 1-3 months from the first symptom onset. Symptoms lasting for > 3 months from the first symptom onset.

Two Cases:

- A 76 year old man with obesity, DM, HTN admitted to ICU with hypoxemic respiratory failure associated with his CoVID.
 - On a ventilatory fo 75 days
 - Hospital stay of 95 days
 - Multiple issues with stay: coma, kidney failure, deconditioning, neuropathy, CNS disease, respiratory compromise, multiple infections
- A 31 year old woman with no PMH develops acute CoVID.
 - Fevers, body aches, fatigue. No medical help sought
 - 100 days out- fatigue, brain fog, lethargy, depression, hair loss, chest pain

Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity.

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation $\geq 94\%$	Oxygen saturation $< 94\%$; respiratory rate ≥ 30 breaths/min; lung infiltrates $> 50\%$	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis					
Potential Treatment					
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Virus vs General response to being ill

- Post ICU syndrome
 - Common to all prolonged ICU stays regardless of etiology. Clear research on this
- Reactive process from COVID
 - Loss of taste, chronic illness, depression
- ME/CFS- Clear patterns with PASC and ME/CFS
- From COVID specifically
 - May be all symptoms?
 - The presence in minimally symptomatic argues SARS-CoV-2

Symptoms associated with PASC

A broad collection

- Constitutional
 - Fatigue
 - Joint pain
- Cardiac/Pulmonary
 - Dyspnea
 - Cough
 - Tachycardia
- Neuro/Psych
 - Depression
 - Anxiety
 - Insomnia
 - Anosmia
- GI-dysgusia, anorexia
- Skin-Rash, hair loss, tooth loss, nail damage

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)

How common is this?

Telephone follow up of over 1200 patients

Outcome	Value*
Mortality and rehospitalization	
Died in the 60 d after discharge, n (% of hospital survivors)	84 (6.7)
Rehospitalized, n (% of hospital survivors)	189 (15.1)
Primary care follow-up	
Any follow-up primary care visit in the 60 d after discharge	382
Established PCP	352
New PCP	30
Visit type	
Clinic	77
Telephone	143
Videoconference	161
Days from discharge to visit	
<15	265
15-30	74
>30	37
Home health services	98
New/worsened symptoms	
Persistent symptoms related to illness†	159
New or worsening symptoms related to illness	92
Continued loss of taste and/or smell	64
Cough	75
Shortness of breath/chest tightness/wheezing	81
Difficulty ambulating due to chest problems	44
Breathlessness walking up stairs	112
Oxygen use	32
New use of CPAP or other breathing machine when asleep	34
Return to normal activity	
Unable to return to normal activity	188
New or worsening difficulty completing activities of daily living‡	58
Return to employment	
Employed full- or part-time before COVID-19 hospitalization	195
Able to return to work by 60 d after discharge	117
Median days from discharge to work return (IQR)	27 (13-42)
Reduced hours and/or modified duties upon return to work due to health	30
Unable to return to work	78
Because of health	45
Because of job loss	21
Emotional impact	
Emotionally affected at least mildly by health conditions	238
Emotionally affected at least moderately by health conditions	124
Health care use related to mental health	28
Financial loss/impact	
Financially affected at least mildly by health conditions	179
Financially affected at least moderately by health conditions	124
Specific financial effects	
Used up all or most of savings	47
Unable to pay for necessities, such as food, heat, and housing	29
Contacted by a collection agency	17
Skipped or delayed getting medical care because of cost	16
Took less medication than was prescribed because of cost	11

COVID-19 = coronavirus disease 2019; CPAP = continuous positive airway pressure; IQR = interquartile range; PCP = primary care physician.
 * Values are numbers of patients unless otherwise indicated.

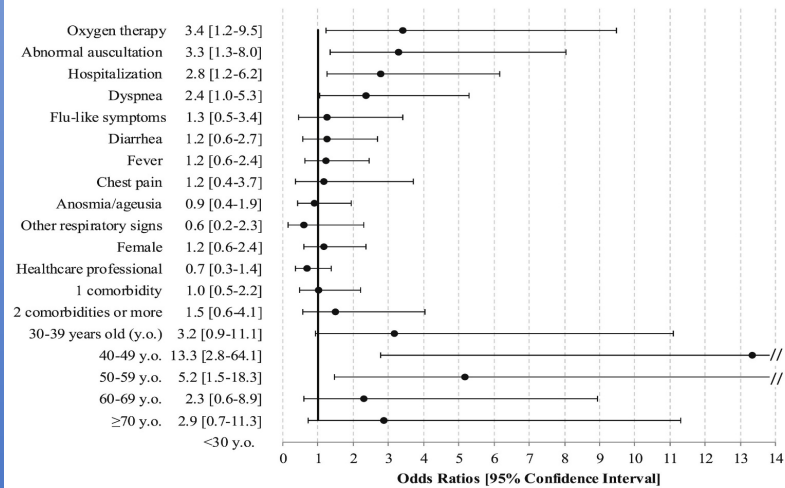
† Include cough, shortness of breath, chest tightness, wheezing, difficulty getting around the house due to chest trouble, breathlessness walking up stairs, oxygen use, and CPAP or other breathing machine use when asleep.

‡ Include dressing, eating, bathing, toileting, transferring in/out of bed, and walking across a room.

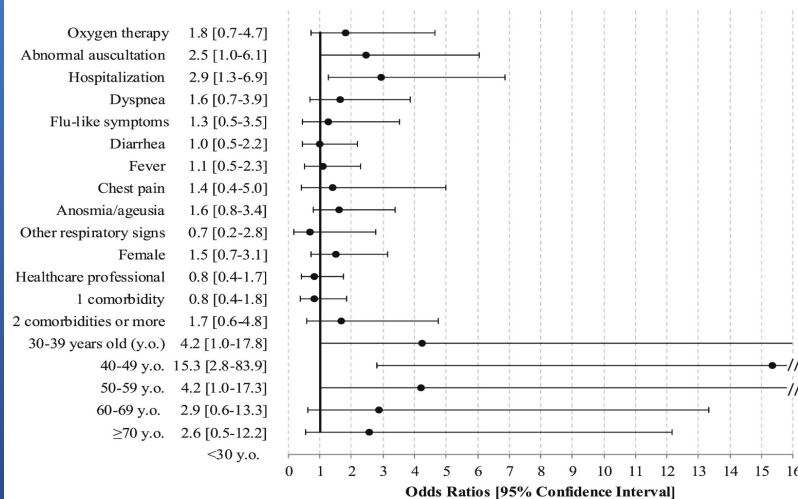
- 1200 patients
- 60 day follow up by phone
- High rates of
 - Ongoing symptoms
 - Employment issues
 - Financial strain

60 day follow up Cohort

Day 30

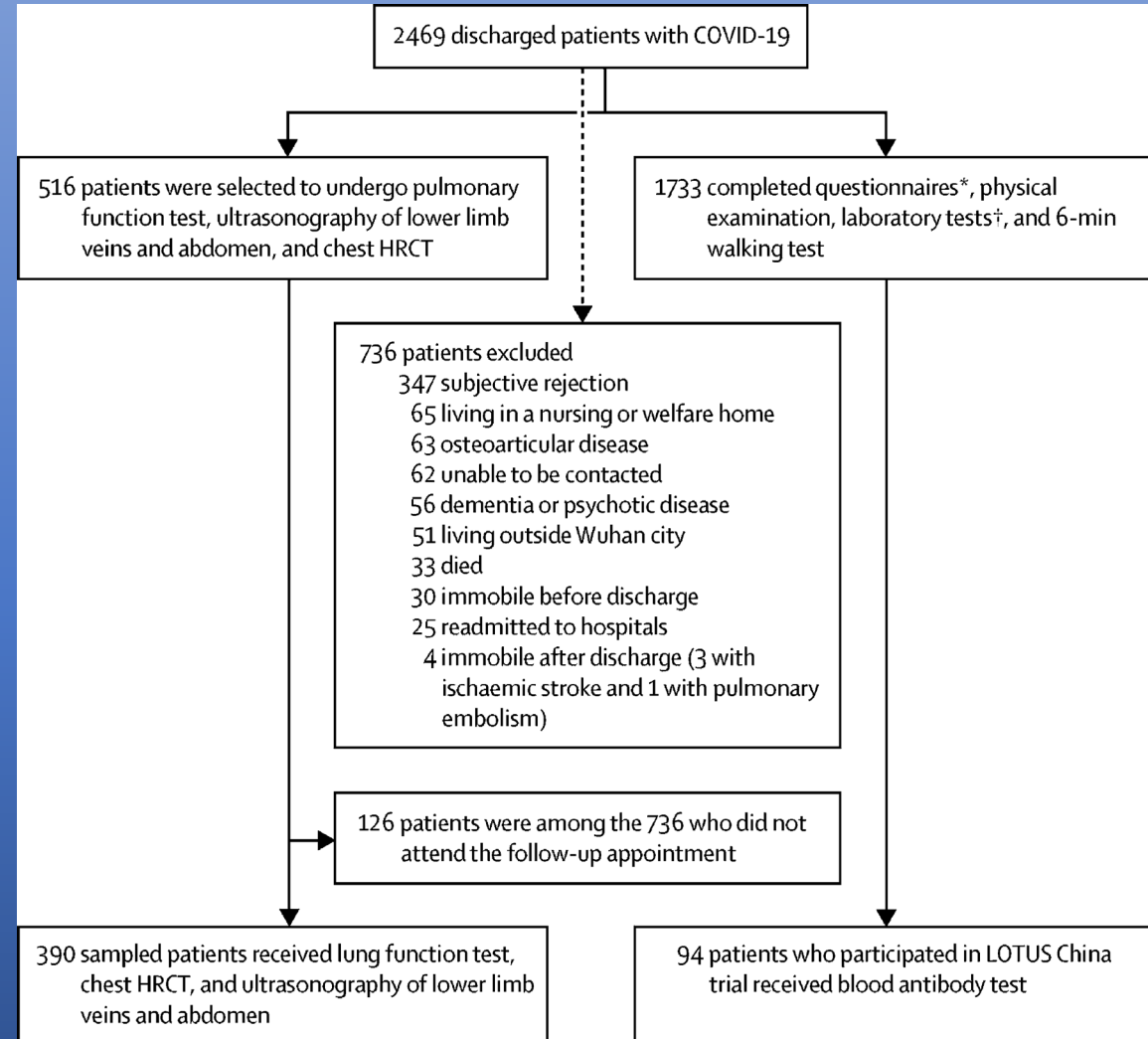


Day 60



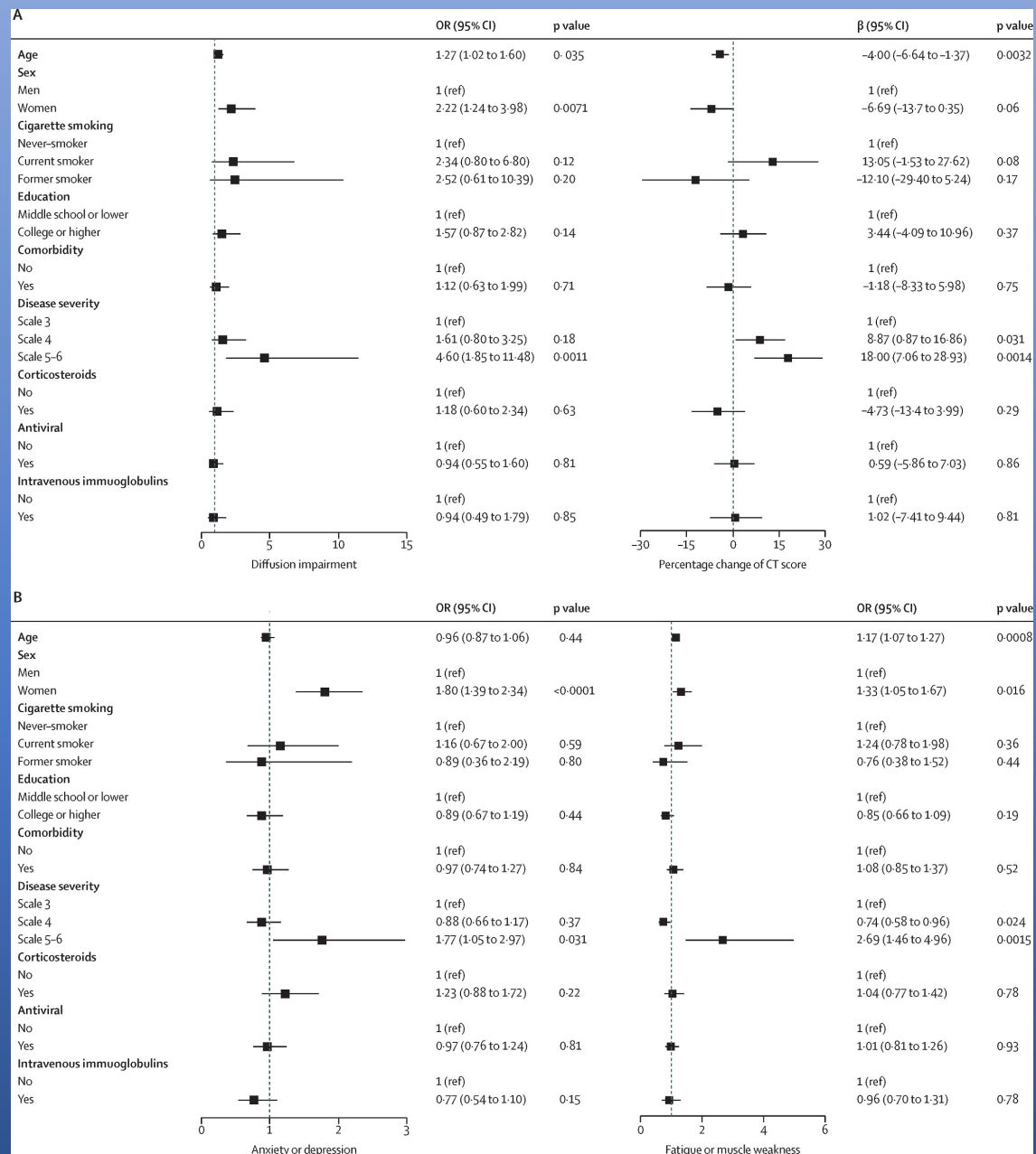
- 293 patients hospitalized
- 30 and 60 day follow up by phone
- Most with mild-moderate disease (34 severe)
- 66% with symptoms
 - Anosmia
 - DOE
 - Asthenia
- Risk: Younger age
- Many healthcare workers

How common is this?

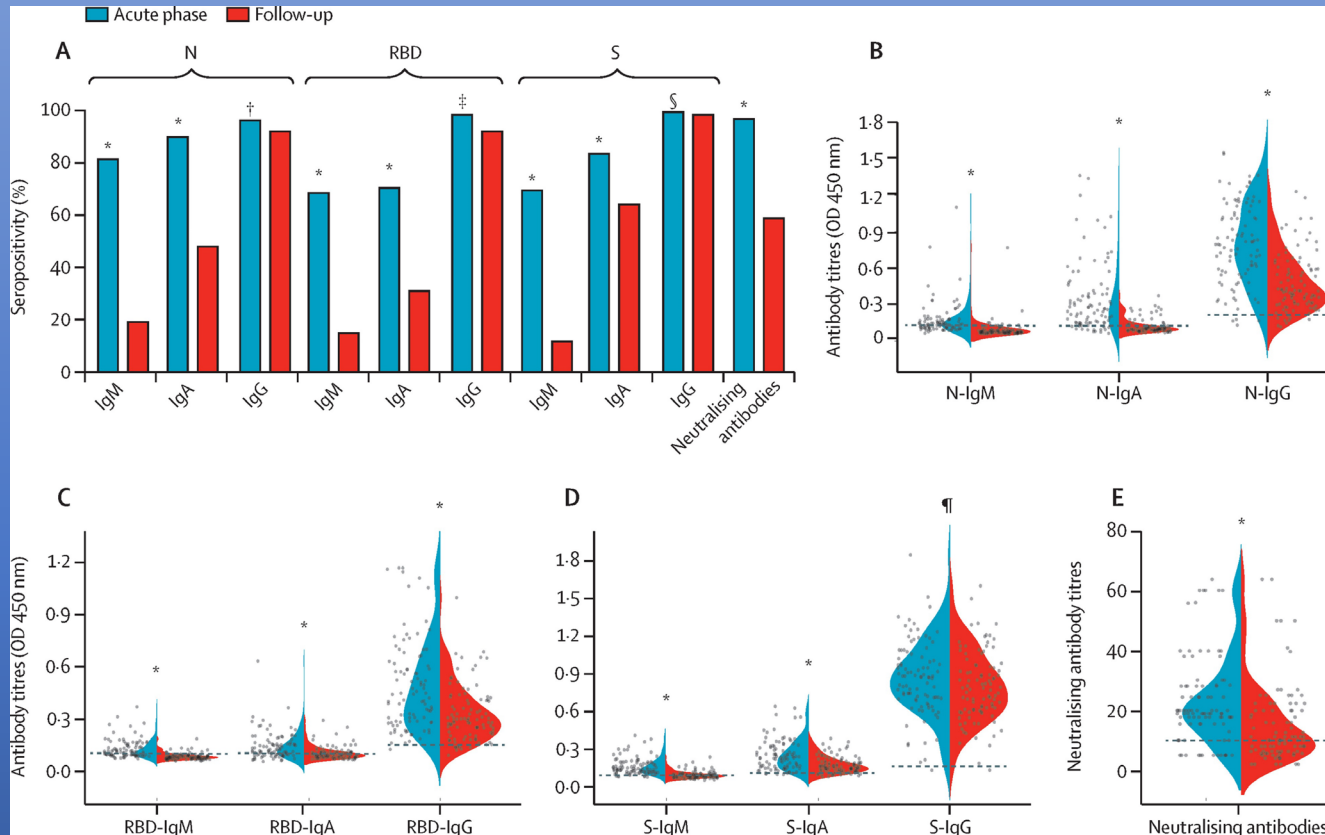


How common is this?

- Key issues:
 - Hospital DC only
 - Most severe will get additional testing (scale 5-6)
- 76% reported symptoms at 180 days
 - Fatigue (63%)
 - Sleep disturbance (26%)
 - Hair loss (22%)
 - Loss of smell/taste (11%)
- 58.6% seropositivity (92% acute phase)
- More severe disease associated with
 - Worsened diffusing capacity
 - Anxiety and depression
 - Fatigue

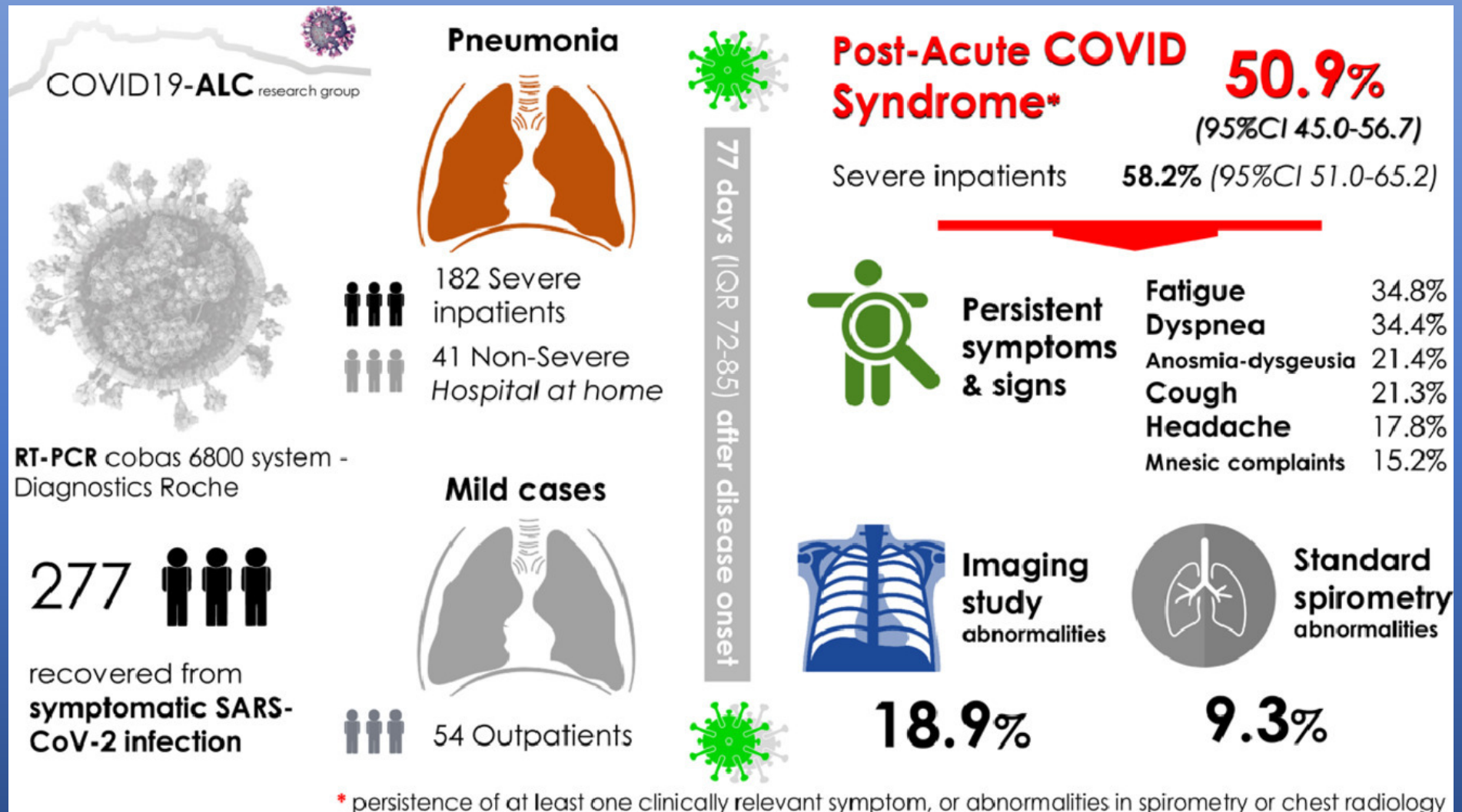


- Severe symptoms
- Female sex



- Antibodies are common acutely
- At 180 days, 58% have detectable antibodies
- Implications for diagnosis and testing

Some mild patients have been studied



From: **Sequelae in Adults at 6 Months After COVID-19 Infection**

JAMA Netw Open. 2021;4(2):e210830. doi:10.1001/jamanetworkopen.2021.0830

- All not hospitalized
- 57% women
- 60% sought no medical attention
- <10% admitted
- Average 170 d from disease onset

Characteristic	No. (%)				
	Total recovered individuals (n = 177)	Inpatients (n = 16)	Outpatients (n = 150)	Asymptomatic individuals (n = 11)	Healthy controls (n = 21)
Age, mean (SD), y	48.0 (15.2)	54 (15.1)	46.3 (14.3)	63.8 (18.8)	50.8 (15.8)
Sex					
Women	101 (57.1)	8 (50.0)	87 (58.0)	6 (54.5)	11 (52.4)
Men	76 (42.9)	8 (50.0)	63 (42.0)	5 (45.5)	10 (47.6)
BMI, mean (SD)	27.1 (5.8)	28.7 (9.1)	26.4 (6.6)	26.3 (5.4)	25.2 (7.1)
Race/ethnicity					
Non-Hispanic/Latino					
White	135 (76.3)	6 (37.5)	121 (80.7)	8 (72.7)	16 (76.2)
Black	3 (1.7)	1 (6.2)	2 (1.3)	0	0
Other ^a	31 (17.5)	8 (50.0)	21 (14.0)	2 (18.2)	5 (23.8)
Hispanic/Latino	7 (4.0)	1 (6.2)	5 (3.3)	1 (9.1)	0
Missing	1 (0.6)	0	1 (0.7)	0	0
Influenza vaccination	130 (73.4)	12 (75.0)	109 (72.7)	9 (81.8)	18 (85.7)
Comorbidities					
Hypertension	23 (13.0)	3 (18.8)	18 (12.0)	2 (18.2)	0
Diabetes	9 (5.1)	4 (25.0)	4 (2.7)	1 (9.1)	1 (4.8)
Active smoking	8 (4.5)	0	7 (4.7)	1 (9.1)	1 (4.8)
Highest level of care accessed during acute illness					
None	107 (60.5)	0	96 (64.0)	11 (100)	21 (100)
Primary care	37 (20.9)	0	37 (24.7)	0	0
Urgent room or emergency department	17 (9.6)	0	17 (11.3)	0	0
Admitted to hospital or ICU	16 (9.0)	16 (100)	0	0	0
Post-COVID-19 follow-up characteristics					
Time after illness onset, median (SD), d ^b	169 (39.5)	179 (44.9)	169 (37.1)	139 (47.1)	87 (31.3)
Persistent symptoms ^c					
0	119 (67.2)	10 (62.5)	98 (65.3)	11 (100.0)	20 (95.2)
1-2	29 (16.4)	2 (12.5)	28 (18.7)	0	0
≥3	24 (13.6)	3 (18.8)	21 (14.0)	0	1 (4.8)
Missing	7 (4.0)	1 (6.3)	3 (2.0)	0	0
Worsened quality of life ^d	53 (29.9)	7 (43.8)	44 (29.3)	2 (18.2)	2 (9.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COVID-19, coronavirus disease 2019; ICU, intensive care unit.

^a Other race/ethnicity included American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and more than 1 race.

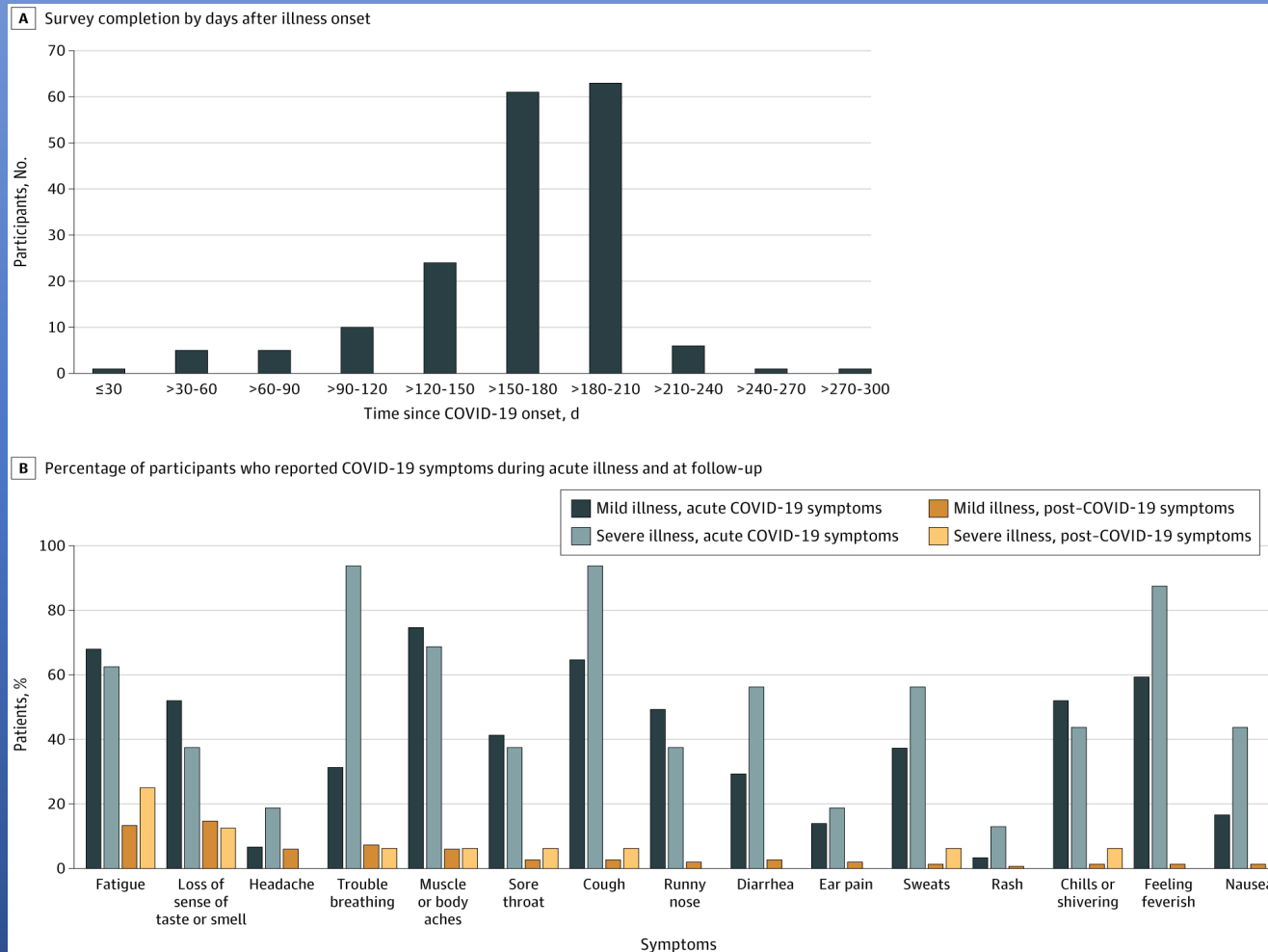
^b Time since symptom onset in severe/mild cohorts, time since first positive test in asymptomatic individuals, time since enrollment in healthy controls.

^c Participants with COVID-19 were asked whether they experienced continued symptoms from their COVID-19 illness. Healthy patients in the control group were asked whether they experienced symptoms from an illness at the time of follow up survey completion.

^d Quality of life was assessed using a sliding scale ranging from 0 (worst imaginable health) to 100 (best imaginable health). Worsened quality of life was defined as a 10-point decrease in health status from before COVID-19 to the time of survey completion.

From: **Sequelae in Adults at 6 Months After COVID-19 Infection**

JAMA Netw Open. 2021;4(2):e210830. doi:10.1001/jamanetworkopen.2021.0830



- About 25% reported at least 2 symptoms at 180 days
- Fatigue and loss of smell most common
- Symptoms prior did not correlate with long term symptoms.
- Impact for those minimally involved

Risk factors

TABLE 1. Characteristics of symptomatic outpatients with SARS-CoV-2 real-time reverse transcription–polymerase chain reaction (RT-PCR)—positive test results (N = 270)* who reported returning to usual state of health or not returning to usual state of health at an interview conducted 14–21 days after testing — 14 academic health care systems,† United States, March–June 2020

Characteristic	Total	Returned to usual health, no. (row %)		P-value [§]
		Yes (n = 175)	No (n = 95)	
Sex				0.14
Women	140	85 (61)	55 (39)	
Men	130	90 (69)	40 (31)	
Age group (yrs)				0.010
18–34	85	63 (74)	22 (26)	
35–49	96	65 (68)	31 (32)	
≥50	89	47 (53)	42 (47)	
Race/Ethnicity				0.29
White, non-Hispanic	94	58 (62)	36 (38)	
Black, non-Hispanic	46	26 (57)	20 (43)	
Other race, non-Hispanic	32	24 (75)	8 (25)	
Hispanic	98	67 (68)	31 (32)	
Insurance (14 missing)				0.69
No	46	31 (67)	15 (33)	
Yes	210	135 (64)	75 (36)	
No. of medical conditions (7 missing)				0.003
0	123	87 (71)	36 (29)	
1	57	41 (72)	16 (28)	
2	39	21 (54)	18 (46)	
≥3	44	19 (43)	25 (57)	
Individual medical conditions (7 missing all) [¶]				
Hypertension	64	33 (52)	31 (48)	0.018
Obesity (body mass index >30 kg/m ²)	51	23 (45)	28 (55)	0.002
Psychiatric condition	49	23 (47)	26 (53)	0.007
Asthma	36	23 (64)	13 (36)	0.99
Diabetes	28	16 (57)	12 (43)	0.43
Immunosuppressive condition	15	6 (40)	9 (60)	0.047
Autoimmune condition	13	7 (54)	6 (46)	0.44
Blood disorder	8	4 (50)	4 (50)	0.47
Chronic kidney disease	7	3 (43)	4 (57)	0.26
Chronic obstructive pulmonary disease	7	4 (57)	3 (43)	0.71
Liver disease	6	4 (67)	2 (33)	1.00
Neurologic condition	6	3 (50)	3 (50)	0.48
Coronary artery disease	4	3 (75)	1 (25)	1.00
Congestive heart failure	2	2 (100)	0 (0)	0.54

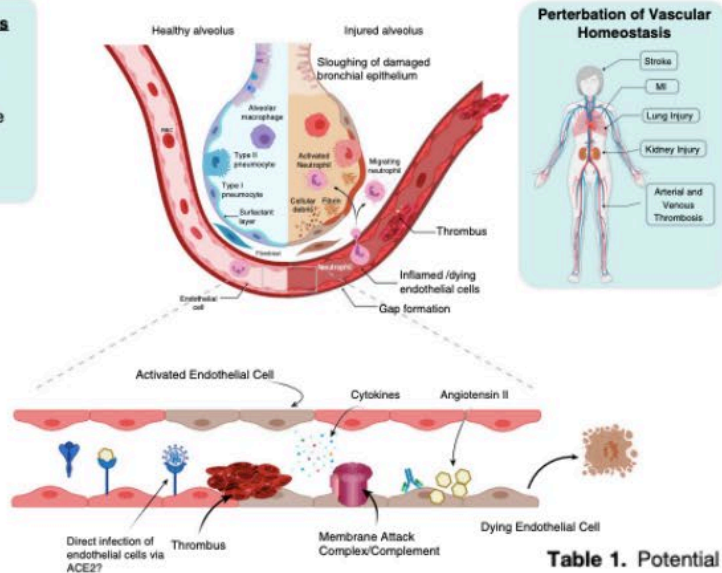
* 270 patients were included in the analysis. † Study conducted at 14 academic health care systems in the United States. ‡ SARS-CoV-2 real-time reverse transcription–polymerase chain reaction (RT-PCR)–positive test results. § P-value for chi-square test. ¶ All missing data were excluded from the analysis.

- Hard to know as not many studies
- Severe disease and comorbidities
- More likely older but bias with severity
- Female, pre-existing mental health illness but bias
- Ongoing ROA to be submitted

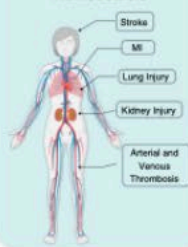
CORRESPONDENCE

Risk Factors

Age
Diabetes
HTN
CV disease
Obesity
ABO



Perurbation of Vascular Homeostasis



COVID-19-associated Acute Respiratory Distress Syndrome Clarified: A Vascular Endotype?

Nilam S. Mangalmurti, M.D.*

John P. Reilly, M.D., M.S.C.E.

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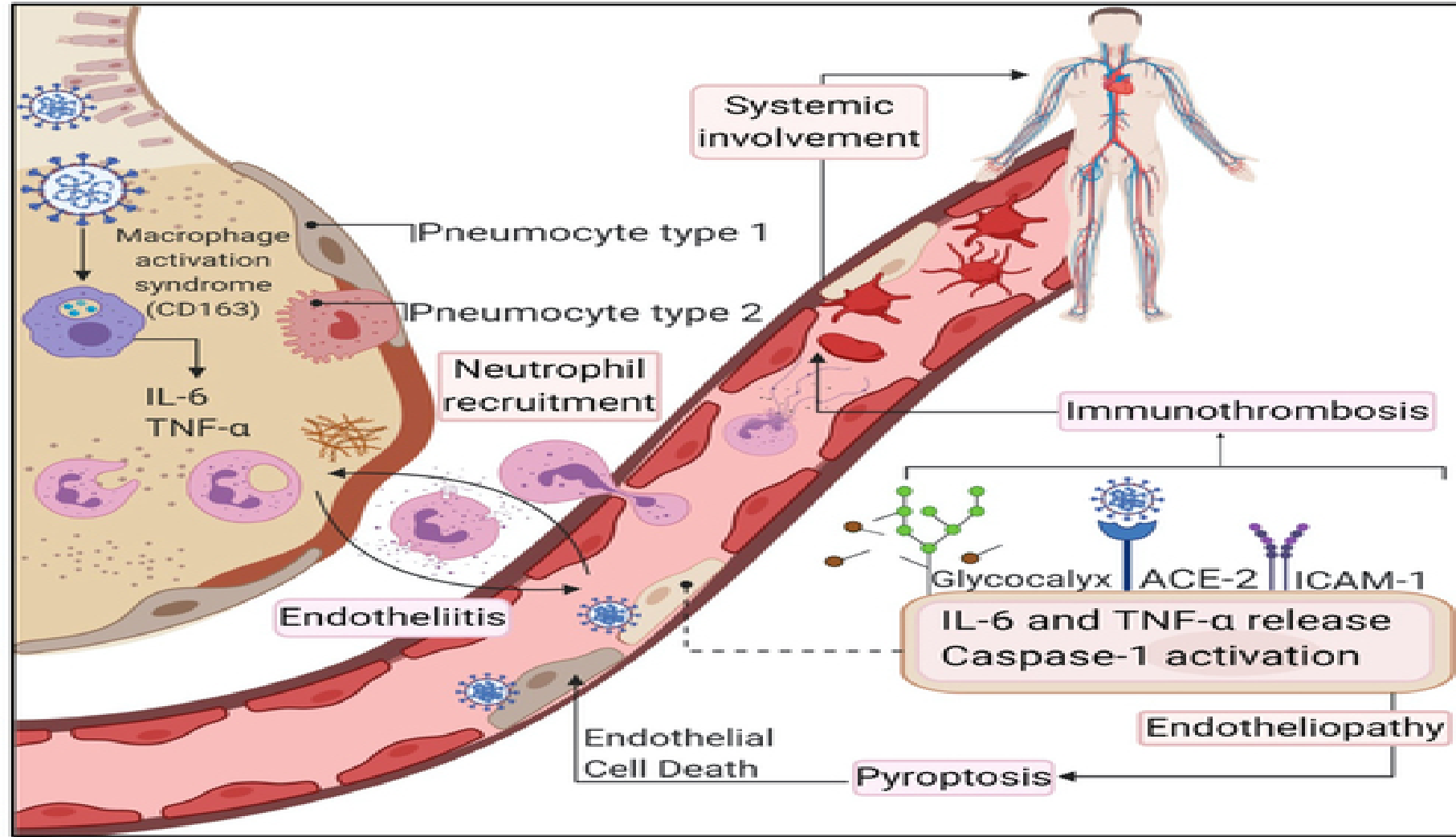
American Journal of Respiratory and Critical Care Medicine Volume 202

Number 5 | September 1 2020

Table 1. Potential Vascular Complications in Critically Ill Patients with COVID-19

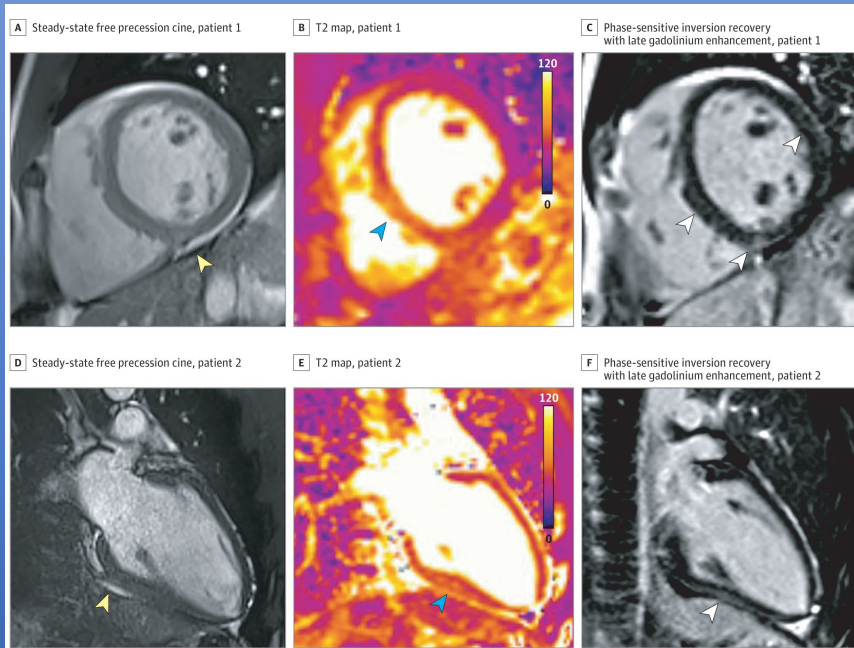
	Complication	Organ Affected
Macrovascular	Deep vein thrombosis	Extremities, pelvic
	Pulmonary embolism	Lung
Arterial	<i>In situ</i> pulmonary thrombosis*	Lung
	Stroke	CNS
	Myocardial infarction	Heart
	Mesenteric ischemia	Gut
	Limb Ischemia	Extremities
Microvascular	Thrombosis	Lung, heart, intestines, kidneys, and skin
Extracorporeal	ECMO oxygenator clotting	N/A
	Renal replacement filter clotting	N/A

SARS-CoV-2



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

JAMA Cardiol. 2021;6(1):116-118. doi:10.1001/jamacardio.2020.4916



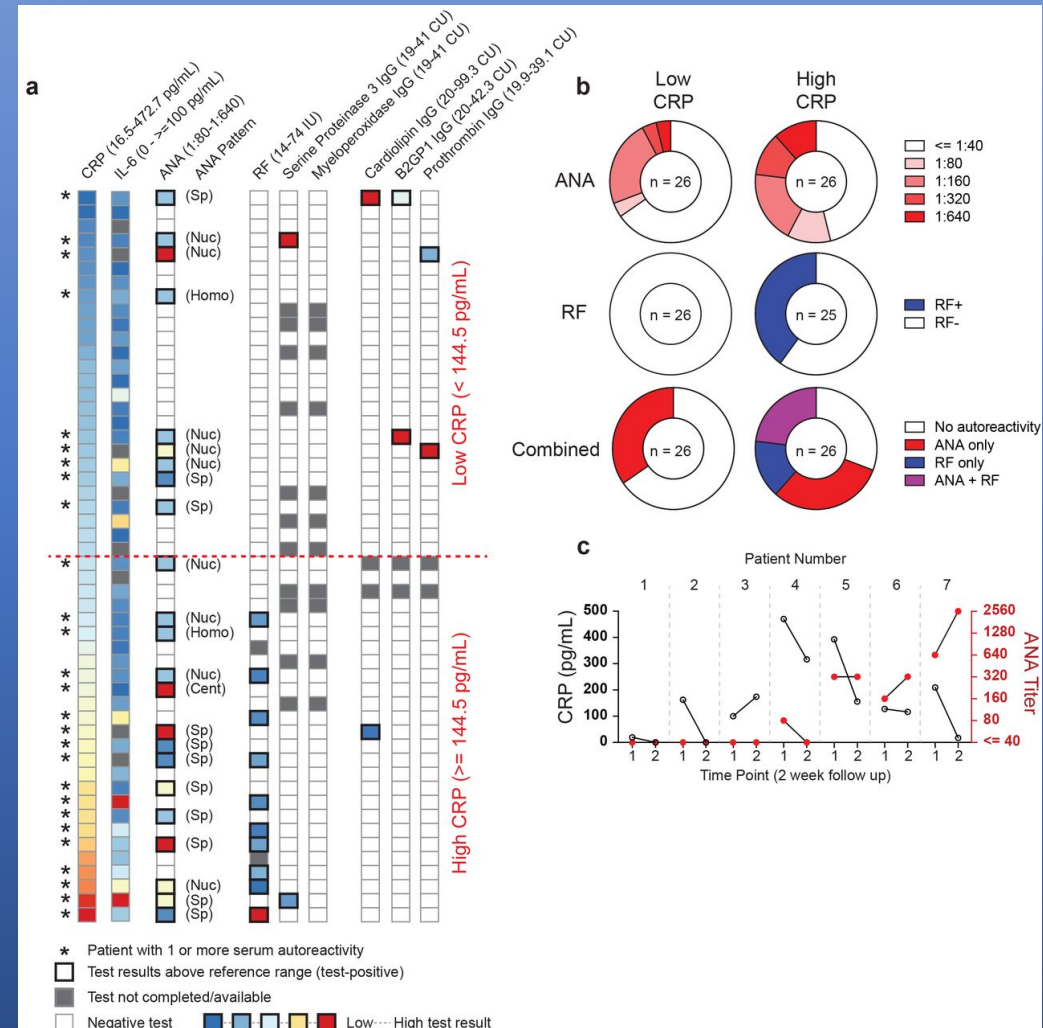
- 10% of patients had active signs of myocardial inflammation
- 25% had signs of prior injury





Autoimmune response with acute inflammation

- Antibodies for autoimmune disease 2 times more likely in COVID with inflammation
- Likely genetic component to phenotypic variability



Pathological Studies of Microvascular Injury in the Brains of Patients Who Died from Covid-19.

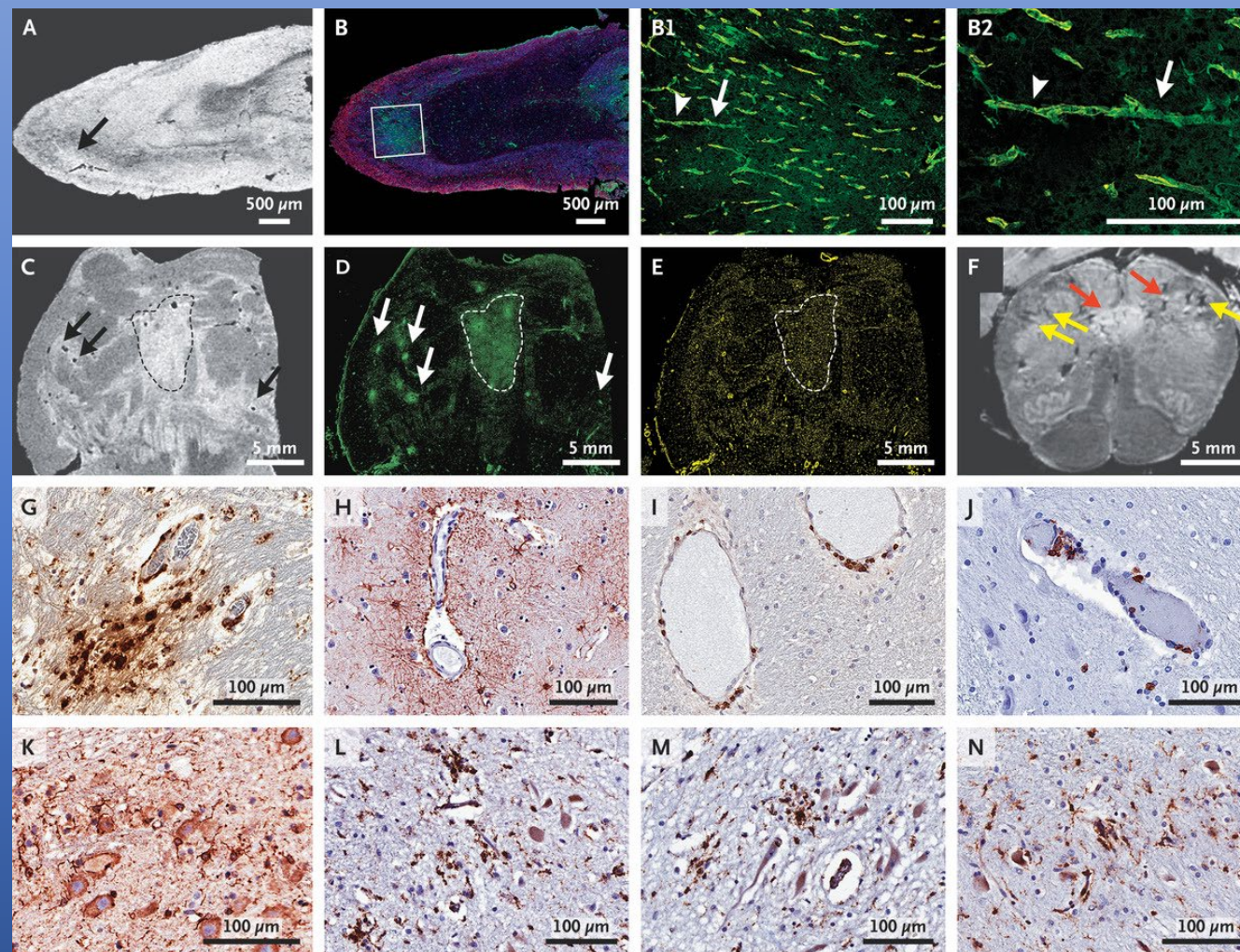
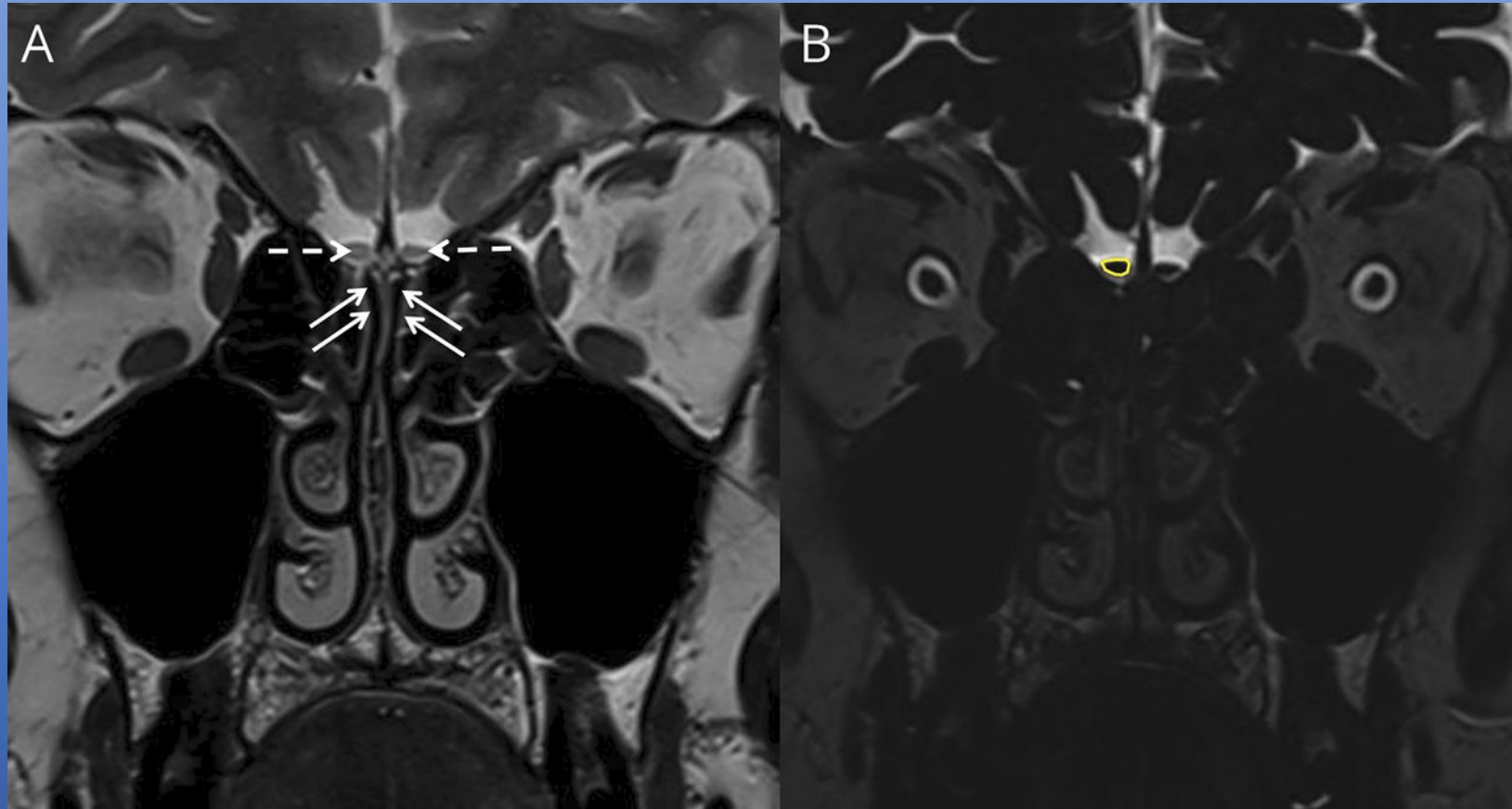


Figure 1 Fifty-two-year-old female healthy control



Michael Eliezer et al. *Neurology* 2020;95:e3145-e3152

UK study evaluating neuropsychiatric symptoms after COVID

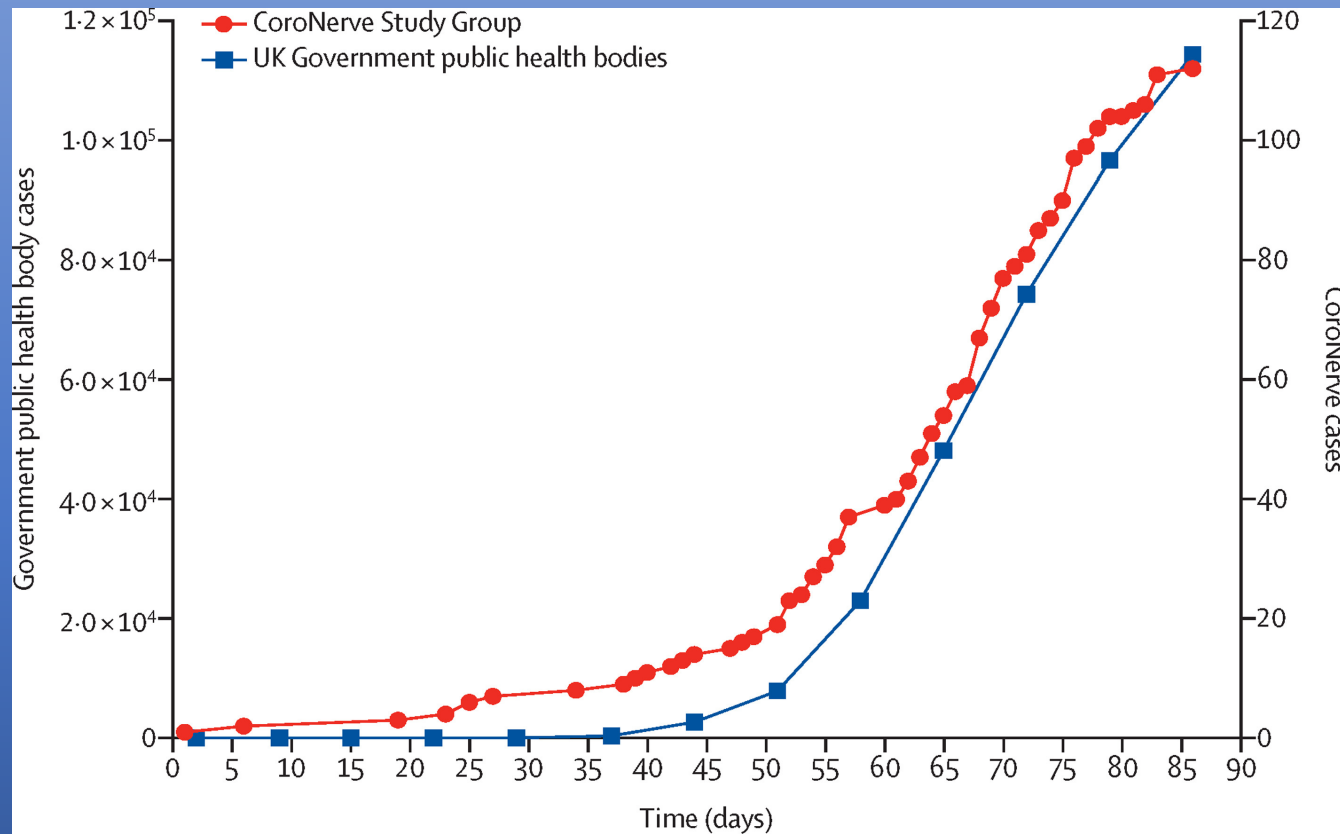
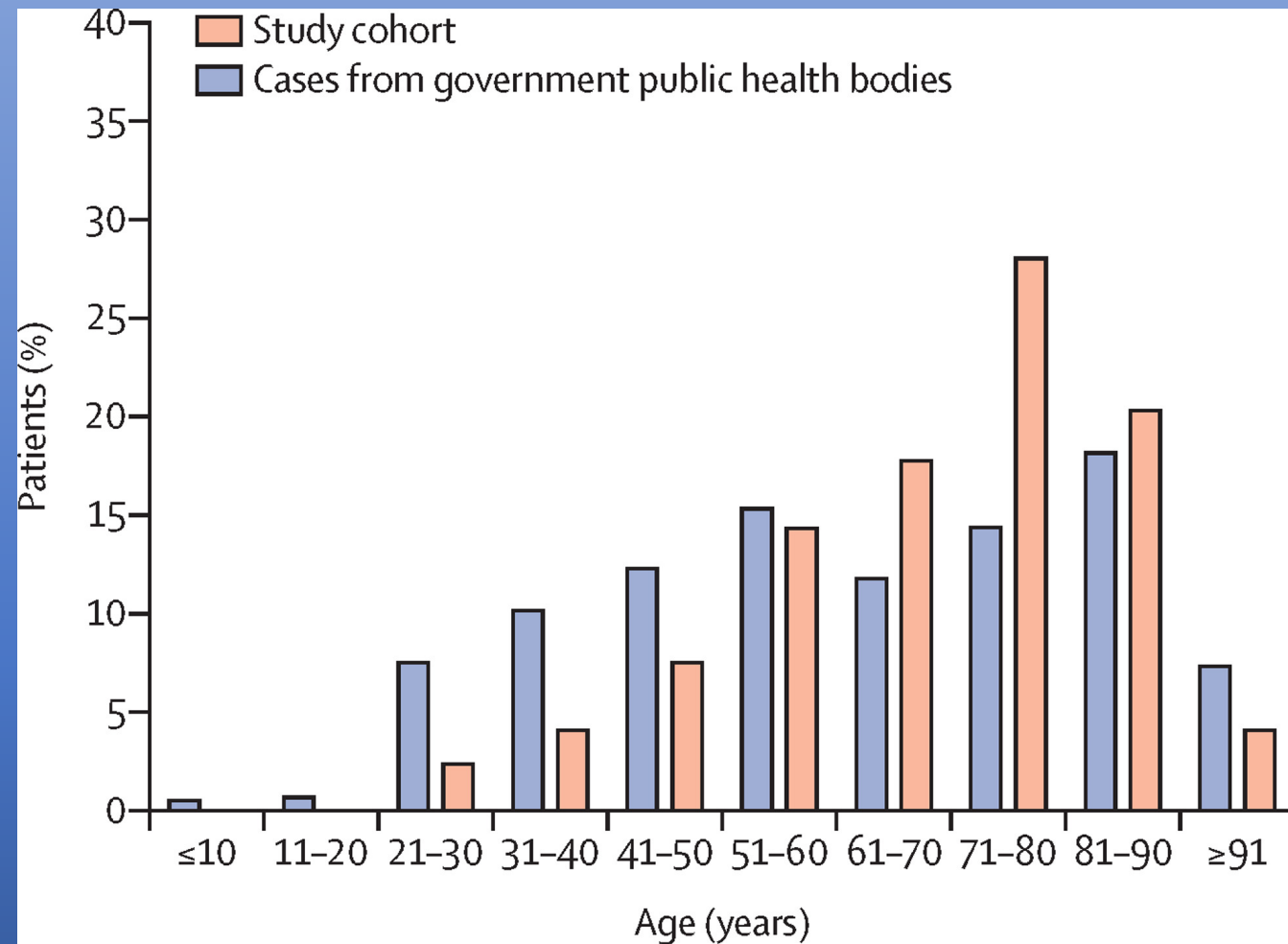


Figure 2



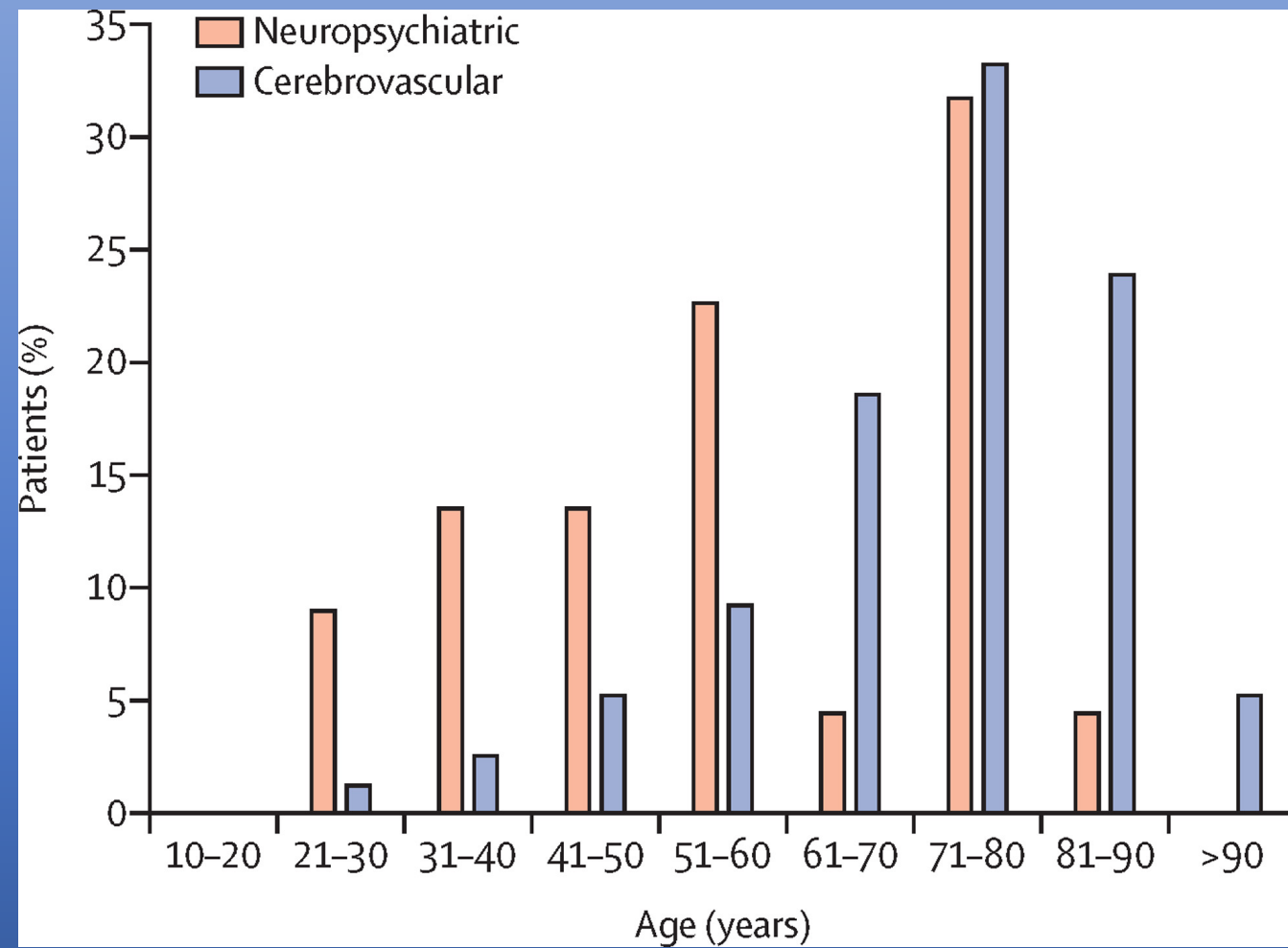
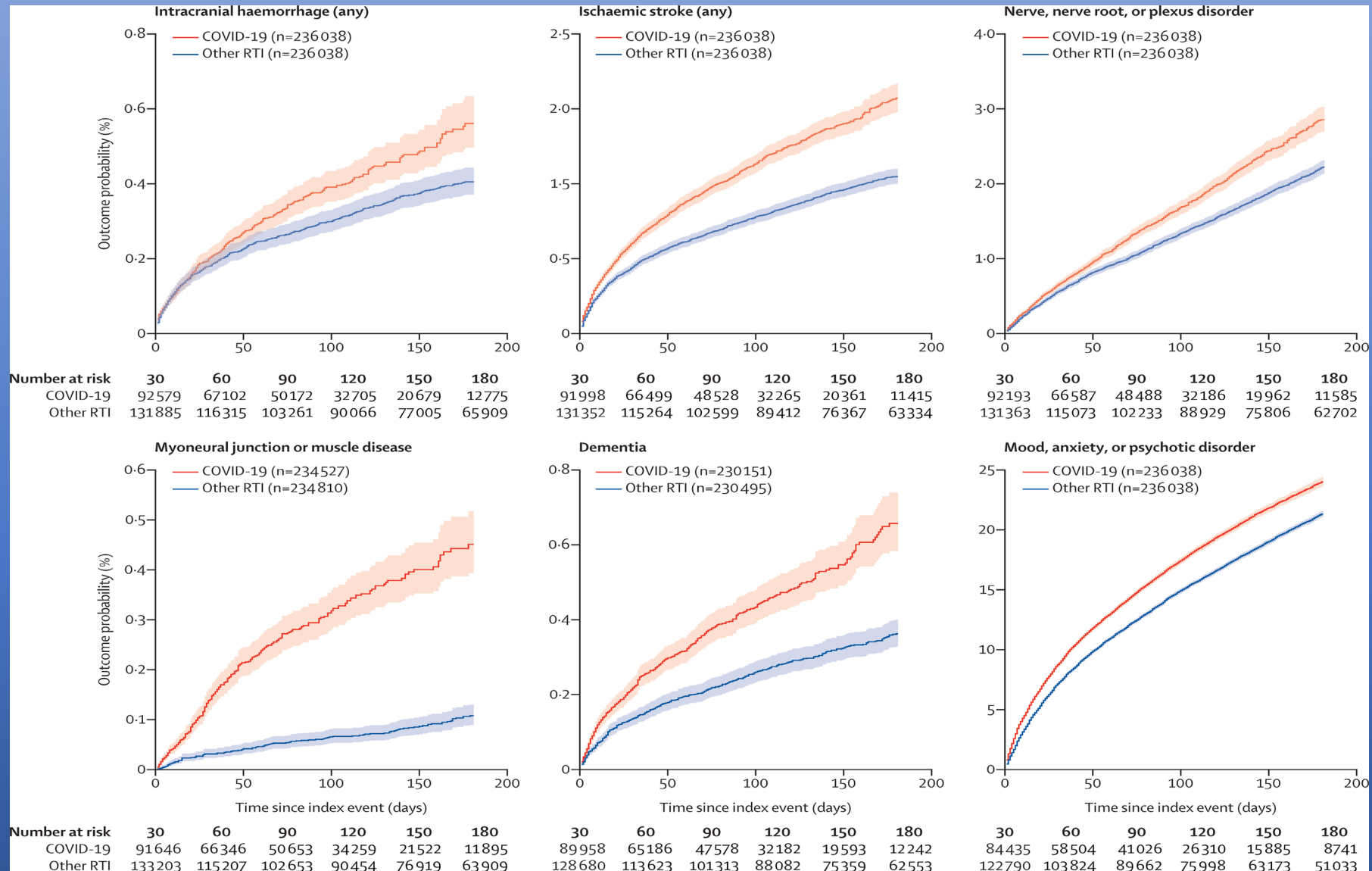
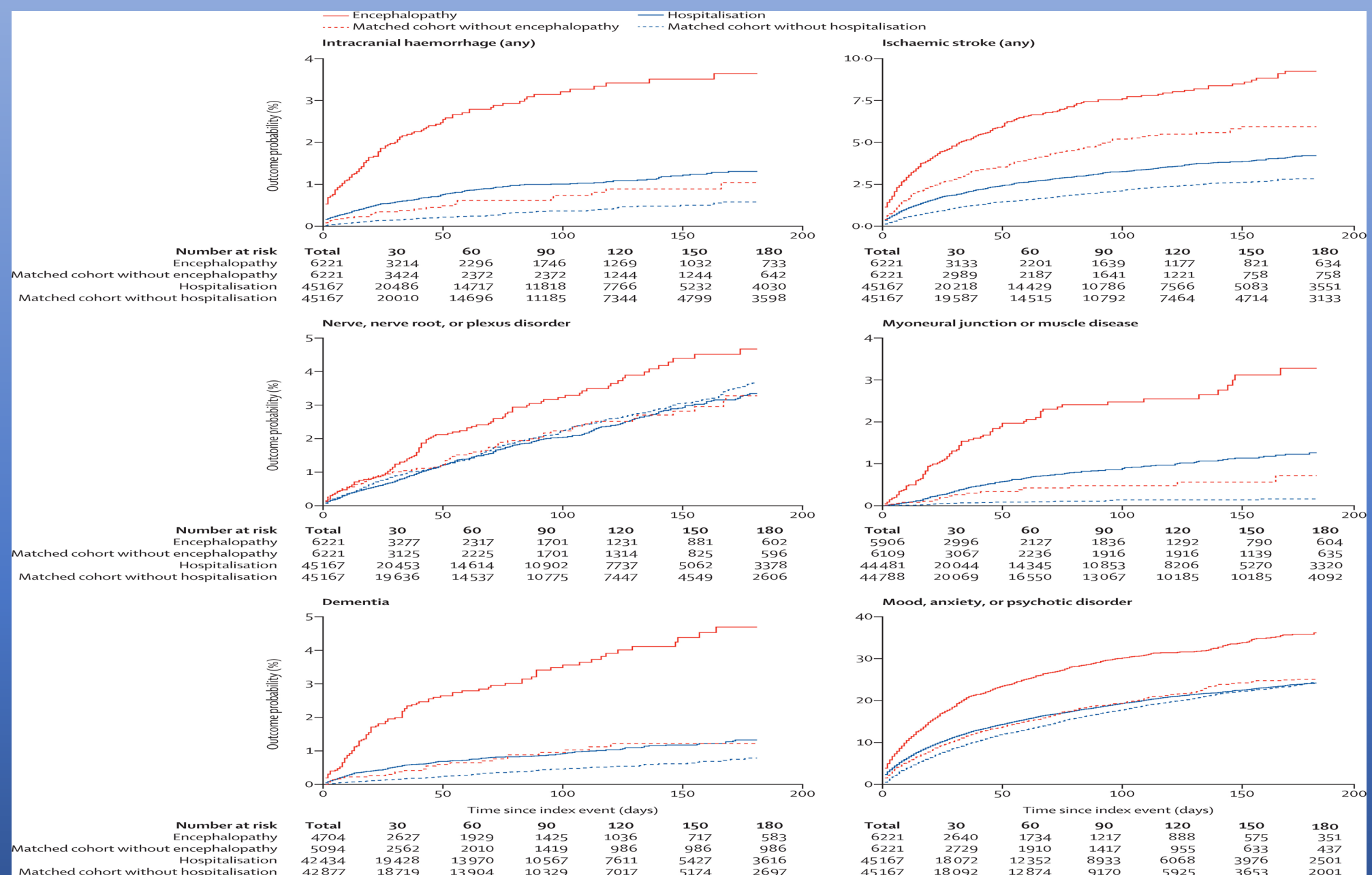


Figure 1

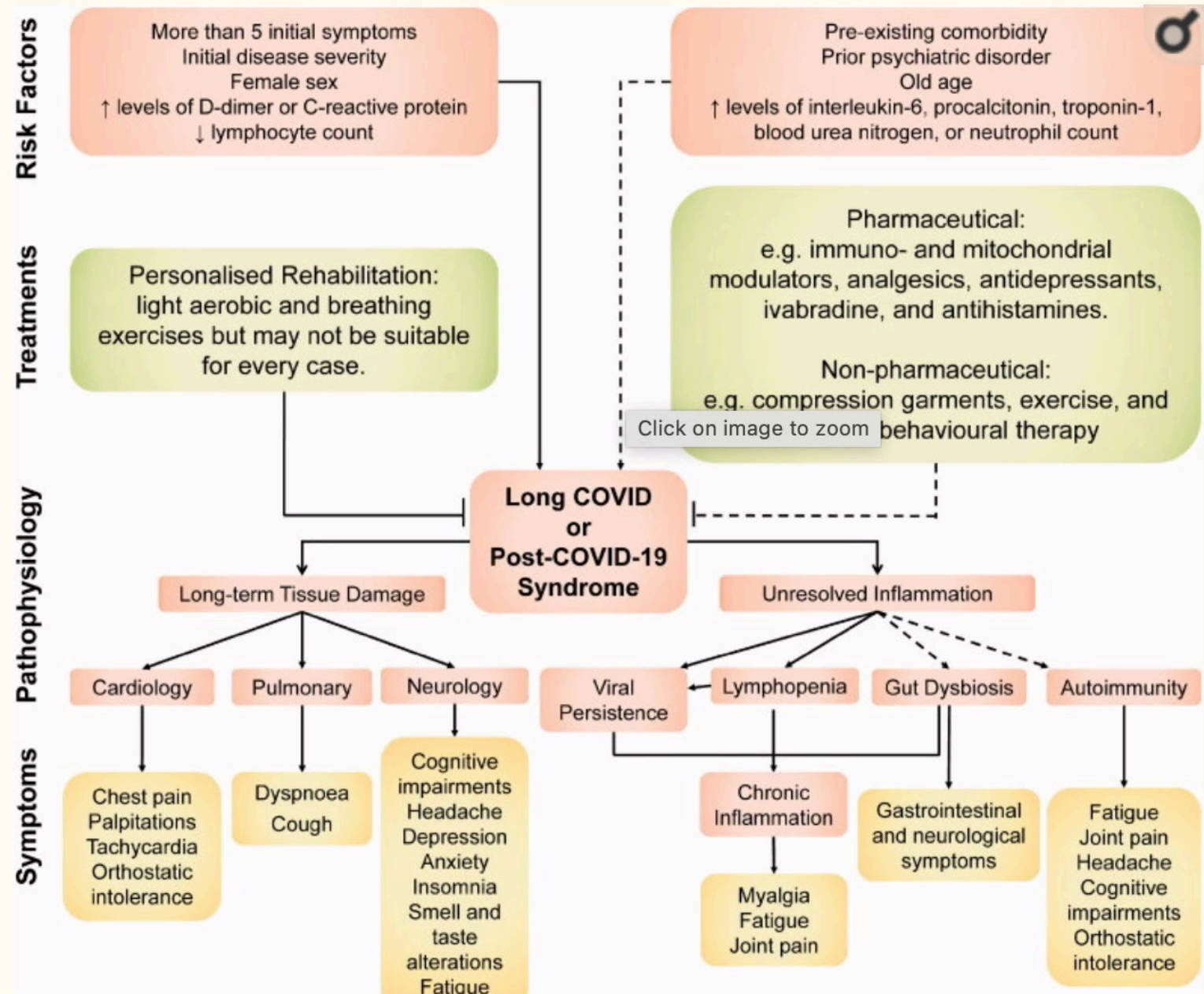




	COVID-19 vs influenza in patients without hospitalisation (N=96 803)*		COVID-19 vs other RTI in patients without hospitalisation (N=183 731)*	
	HR (95% CI)	p value	HR (95% CI)	p value
Intracranial haemorrhage (any)	1.87 (1.25–2.78)	0.0013	1.38 (1.11–1.73)	0.0034
Intracranial haemorrhage (first)	1.66 (0.88–3.14)	0.082	1.63 (1.11–2.40)	0.010
Ischaemic stroke (any)	1.80 (1.54–2.10)	<0.0001	1.61 (1.45–1.78)	<0.0001
Ischaemic stroke (first)	1.71 (1.26–2.33)	0.0003	1.69 (1.38–2.08)	<0.0001
Parkinsonism	2.22 (0.98–5.06)	0.028	1.20 (0.73–1.96)	0.42
Guillain-Barré syndrome	0.90 (0.44–1.84)	0.99	1.44 (0.85–2.45)	0.10
Nerve, nerve root, or plexus disorders	1.69 (1.53–1.88)	<0.0001	1.23 (1.15–1.33)	<0.0001
Myoneural junction or muscle disease	3.46 (2.11–5.67)	<0.0001	2.69 (1.91–3.79)	<0.0001
Encephalitis	1.77 (0.86–3.66)	0.095	2.29 (1.28–4.10)	0.0046
Dementia	1.88 (1.27–2.77)	0.0008	1.95 (1.55–2.45)	<0.0001
Mood, anxiety, or psychotic disorder (any)	1.49 (1.45–1.54)	<0.0001	1.18 (1.15–1.21)	<0.0001
Mood, anxiety, or psychotic disorder (first)	1.85 (1.72–1.99)	<0.0001	1.40 (1.32–1.48)	<0.0001
Mood disorder (any)	1.49 (1.43–1.55)	<0.0001	1.22 (1.19–1.26)	<0.0001
Mood disorder (first)	1.78 (1.61–1.96)	<0.0001	1.37 (1.27–1.47)	<0.0001
Anxiety disorder (any)	1.48 (1.43–1.54)	<0.0001	1.16 (1.13–1.19)	<0.0001
Anxiety disorder (first)	1.80 (1.67–1.94)	<0.0001	1.37 (1.30–1.45)	<0.0001
Psychotic disorder (any)	1.93 (1.63–2.28)	<0.0001	1.44 (1.27–1.62)	<0.0001
Psychotic disorder (first)	2.27 (1.56–3.30)	<0.0001	1.49 (1.15–1.93)	0.0016
Substance use disorder (any)	1.26 (1.19–1.33)	<0.0001	1.11 (1.07–1.17)	<0.0001
Substance use disorder (first)	1.21 (1.05–1.38)	0.0054	0.89 (0.81–0.97)	0.013
Insomnia (any)	1.52 (1.42–1.63)	<0.0001	1.18 (1.12–1.24)	<0.0001
Insomnia (first)	2.06 (1.82–2.33)	<0.0001	1.51 (1.38–1.66)	<0.0001
Any outcome	1.47 (1.44–1.51)	<0.0001	1.16 (1.14–1.17)	<0.0001
Any first outcome	1.83 (1.71–1.96)	<0.0001	1.28 (1.23–1.33)	<0.0001

Details on cohort characteristics are presented in the appendix (pp 37–40). HR=hazard ratio. RTI=respiratory tract infection. *Matched cohorts.

Table 4: HRs for the major outcomes in patients without hospitalisation after COVID-19 compared with those after influenza or other RTIs



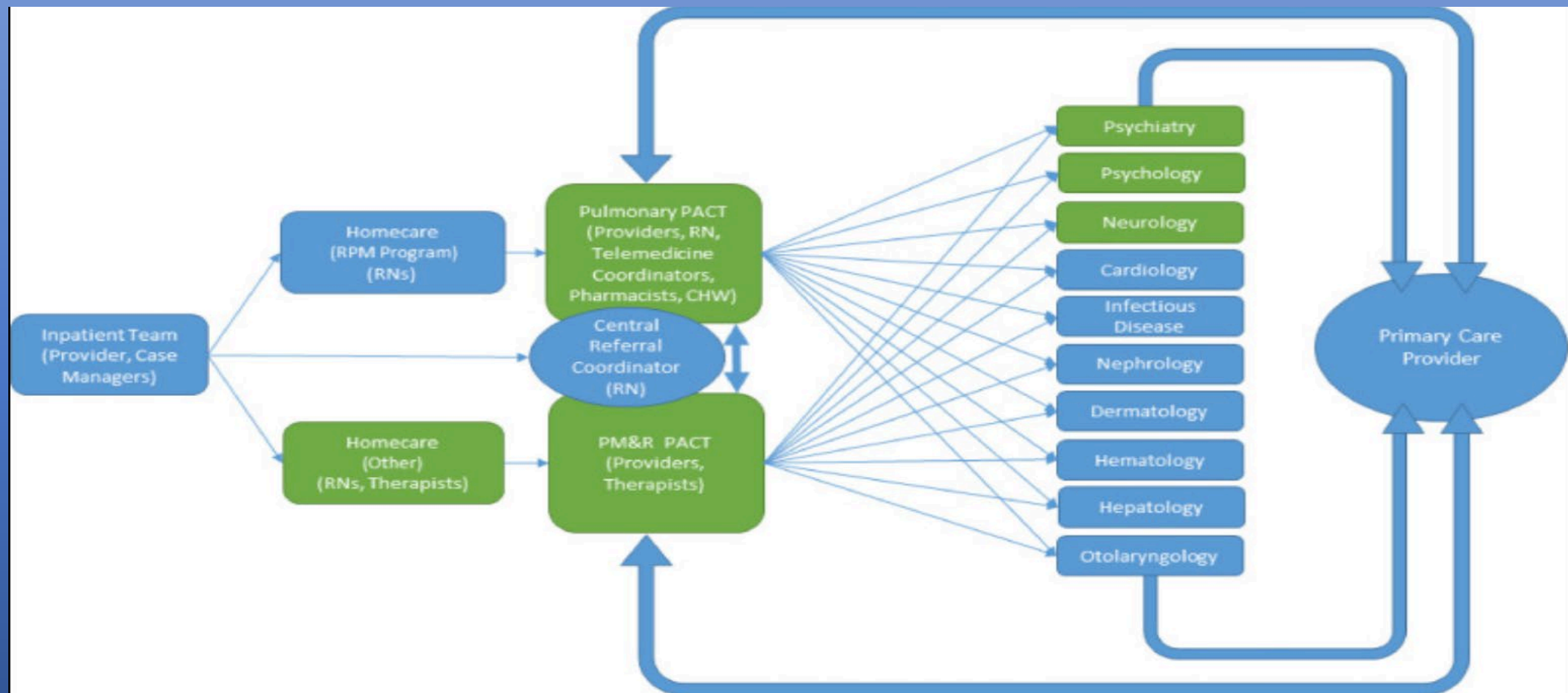
Work up

What are some tests you may consider (after strong history and physical exam)?

- General:
 - CBC, chemistry, D- Dimer, thyroid studies
 - SARS serology NOT recommended
- Dyspnea/Tachycardia/Chest pain- Evaluate exercise and oxygen capacity
 - CXR
 - CT chest with contrast (PE protocol)
 - PFTS
 - EKG and echo (not routine)
 - Cardiopulmonary testing (Very common and needed)

A simple but stupid caveat

- If you have specific illness with screening test abnormality, refer to specialist
 - E.g. Low DLCO or abnormal CT chest- Send to pulmonary
 - Abnormal Montreal cognitive screening- Neuro
- Underlies the value of a multi-disciplinary clinic so these patients are not lost



Treatment

Treatment

- Validation of process
- Time of course and patience- Lay out expectations
- Treat what you see and know
 - Low O2- O2 therapy
 - Large clot- anticoagulation
- Comprehensive rehab- cornerstone of therapy
 - Mental health
 - Sleep hygiene
 - Physical rehab
 - Occupational
- DON'T PUSH IT TOO HARD (this is different than other rehab recs)

Rehabilitation along the continuum of care in COVID-19

Acute

Objectives

- Optimize oxygenation
- Manage secretions
- Prevent complications

Input:

Specialist Respiratory physiotherapist /therapist and/or rehabilitation staff experienced with ICU/HDU setting

Setting: ICU/HDU



Post-acute

Objectives

- Identify and manage impairments for affected functioning domains
- Facilitate safe discharge and onward referral

Input: Multidisciplinary

Setting: Rehabilitation ward/unit, stepdown facility, home



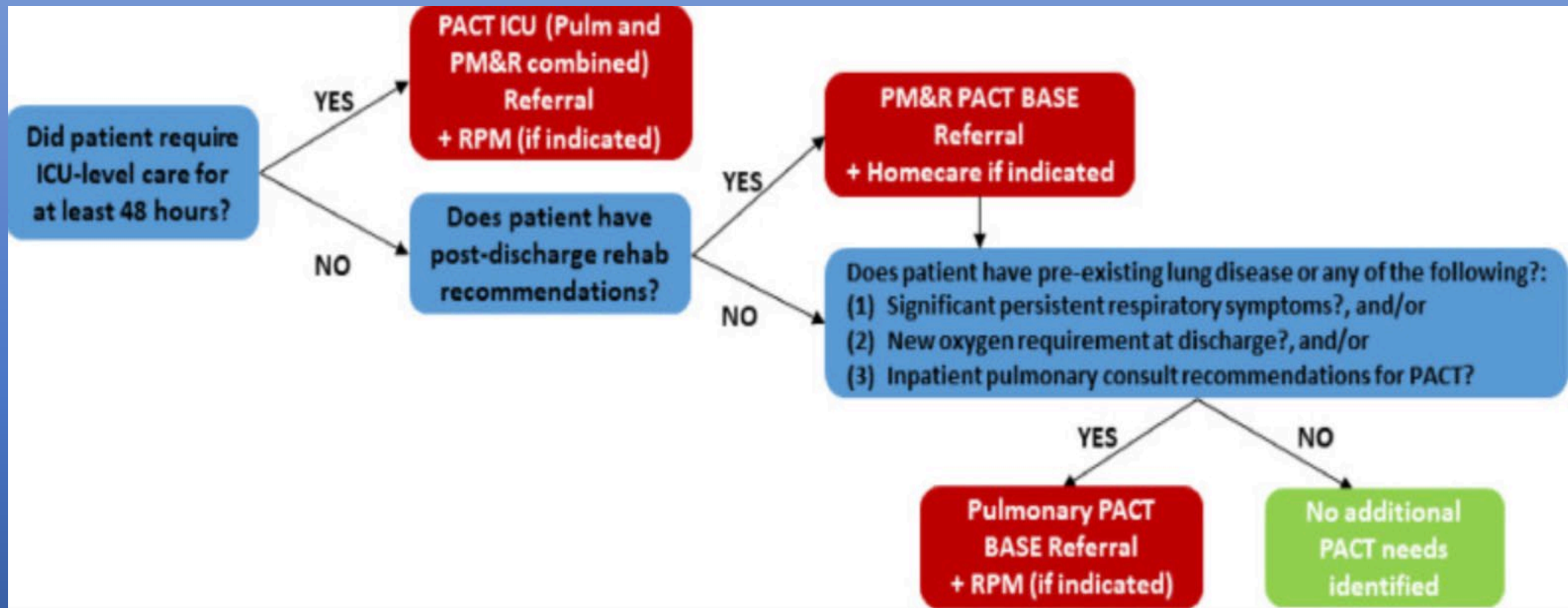
Long-term

Objectives

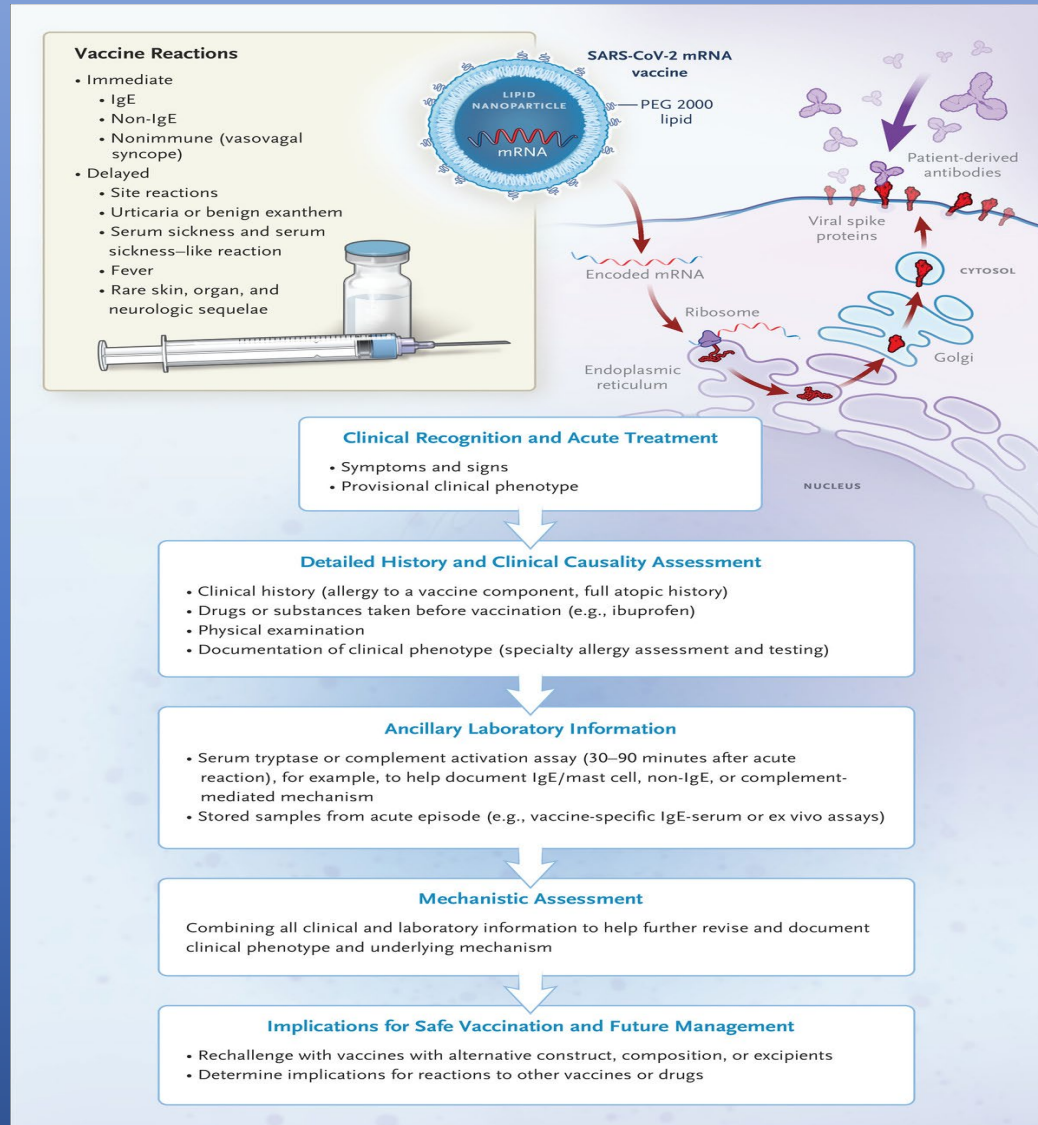
- Optimize functioning/ minimize impact of impairments on independence and quality of life

Input: Multidisciplinary

Setting: Home, outpatient facility, clinic



Assessing Reactions to Vaccines.



- Vaccination in patients with PASC
 - NO DATA
- Anecdotal- Some better, some worse
- What if you have ME/CFS?
- What if you have allergies?
- Vaccine cannot trigger PASC if you don't have it already

Managing these patients/ Employees

- This is a real process and symptoms may be organically explained
- As opposed to other post viral syndromes, we should NOT PUSH them physically
- Testing to rule out other processes
- Consider anticoagulation
- SLOW rehab
- Many might need long times off to recover

