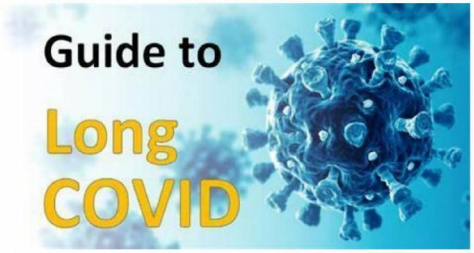

The LONG COVID CONUNDRUM

1) **Definitions and classification**
2) Risk factors
3) Pathophysiology and symptomatology
4) Management

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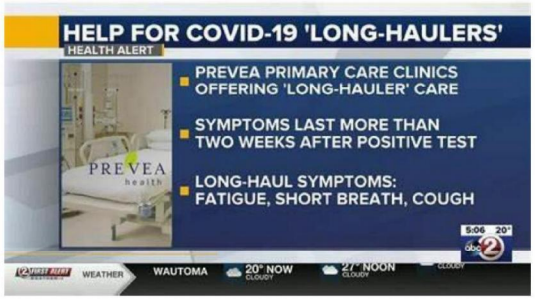


Global Health Institute UA

Timeline for acute and post-acute COVID-19

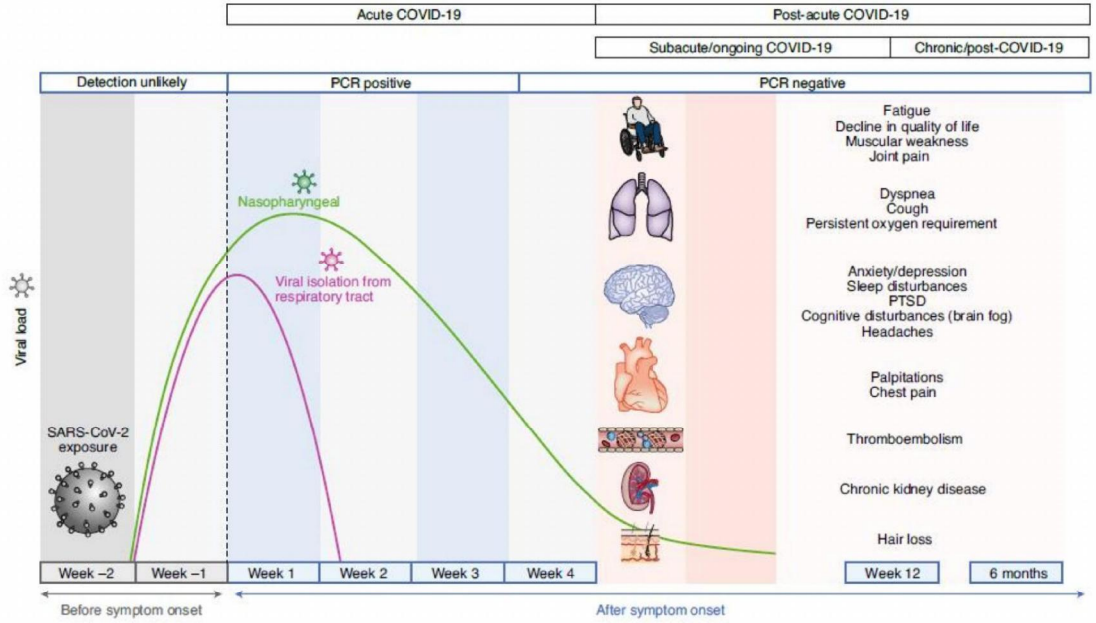


Fig. 1 | Timeline of post-acute COVID-19. Acute COVID-19 usually lasts until 4 weeks from the onset of symptoms, beyond which replication-competent SARS-CoV-2 has not been isolated. Post-acute COVID-19 is defined as persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. The common symptoms observed in post-acute COVID-19 are summarized.

Ref 1 Ani Nalbandian Nat Med April 2021

Terminology and Classification

Terminology: "Long Haulers", Post-Acute COVID-19 Syndrome (PACS), Post-COVID, Chronic COVID or **Long COVID**

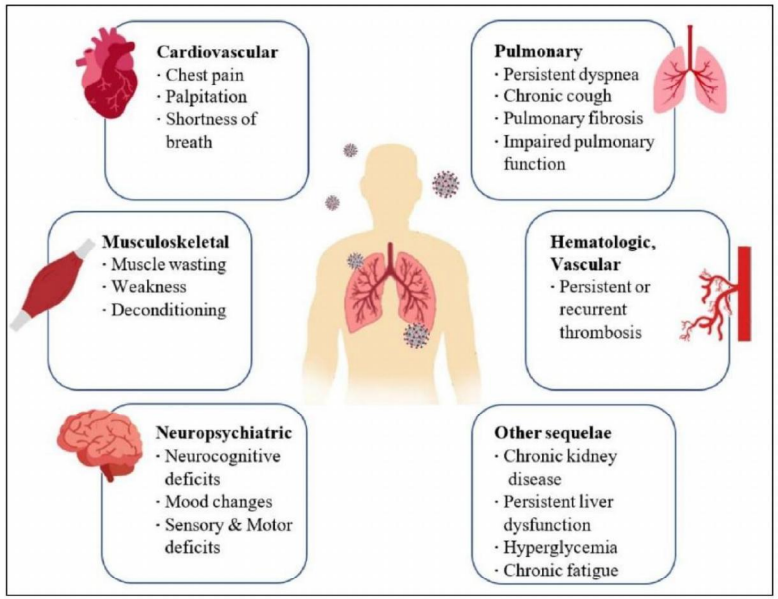
Classification	Reference time point for relapse of COVID-19 symptoms
Classification by NICE (UK) (https://www.nice.org.uk/guidance/ng188)	
Acute COVID-19	<4 Weeks
Ongoing symptomatic COVID-19	4–12 Weeks
Post-COVID-19 syndrome	>12 Weeks
Classification by Fernández-de-Las-Peñas et al. [4]	
Potentially infection related-symptoms	<4–5 Weeks
Acute post-COVID symptoms	Week 5 to Week 12
Long post-COVID symptoms	Week 12 to Week 24
Persistent post-COVID symptoms	>24 weeks

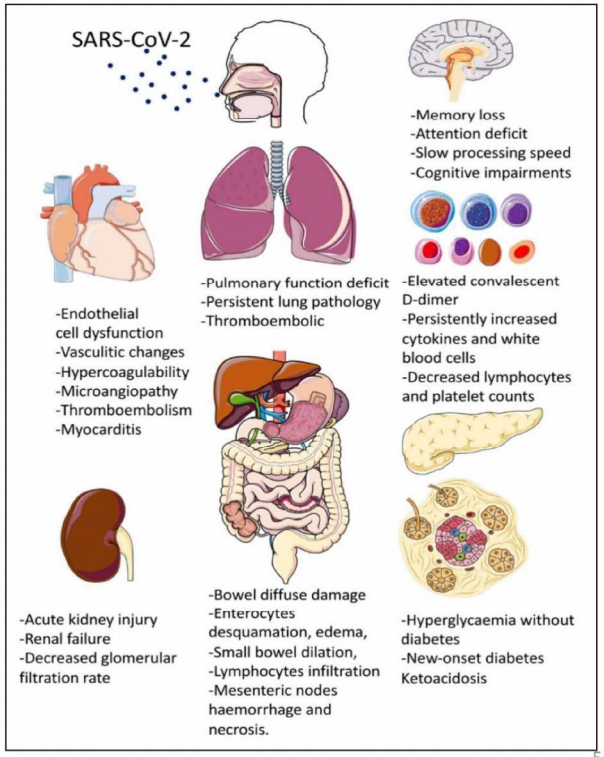
Ref 2 Anushri Umesh Infection 30 April 2022

Long-COVID definitions

Organisation	Definition (Elements)
WHO [7]	*Post-COVID-19 conditions* • Adults with a history of probable or confirmed SARS-CoV-2 infection • ≥3 months from the onset of COVID-19, ≥2 months duration • It cannot be explained by an alternative diagnosis • Clustering of symptoms (fatigue, shortness of breath, and others) • Impact on everyday functioning • Symptoms may be new or persistent after recovery, fluctuate or relapse.
CDC [8] *USA*	• *Post-COVID-19 conditions:* new, returning, or ongoing health problems four or more weeks after COVID-19 • Even people who did not have COVID-19 symptoms initially • These post-COVID-19 conditions may also be known as long COVID-19, long-haul COVID-19, post-acute COVID-19, long-term effects of COVID-19, or chronic COVID-19.
NICE [9] *UK*	• *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. • Long-COVID-19 includes ongoing symptoms and post-COVID-19 syndrome.
AWMF [10] *Germany*	• New or persistent symptoms after the acute COVID-19 phase (>4 weeks) • Health impairment • Worsening of a pre-existing underlying disease.

Multi-system clinical presentation and pathophysiological mechanisms of Long COVID





Ref 4 5.1.2e Pharmaceutics 2022 vol 14 p 1135

Ref 5 5.1.2e Biomedicines Aug 2021

Box 1 | Summary of post-acute COVID-19 by organ system

Pulmonary
- Dyspnea, decreased exercise capacity and hypoxia are commonly persistent symptoms and signs
- Reduced diffusion capacity, restrictive pulmonary physiology, and ground-glass opacities and fibrotic changes on imaging have been noted at follow-up of COVID-19 survivors
- Assessment of progression or recovery of pulmonary disease and function may include home pulse oximetry, 6MWTs, PFTs, high-resolution computed tomography of the chest and computed tomography pulmonary angiogram as clinically appropriate

Hematologic
- Thromboembolic events have been noted to be <5% in post-acute COVID-19 in retrospective studies
- The duration of the hyperinflammatory state induced by infection with SARS-CoV-2 is unknown
- Direct oral anticoagulants and low-molecular-weight heparin may be considered for extended thromboprophylaxis after risk–benefit discussion in patients with predisposing risk factors for immobility, persistently elevated D-dimer levels (greater than twice the upper limit of normal) and other high-risk comorbidities such as cancer

Cardiovascular
- Persistent symptoms may include palpitations, dyspnea and chest pain
- Long-term sequelae may include increased cardiometabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI), arrhythmias, tachycardia and autonomic dysfunction
- Patients with cardiovascular complications during acute infection or those experiencing persistent cardiac symptoms may be monitored with serial clinical, echocardiogram and electrocardiogram follow-up

Neuropsychiatric
- Persistent abnormalities may include fatigue, myalgia, headache, dysautonomia and cognitive impairment (brain fog)
- Anxiety, depression, sleep disturbances and PTSD have been reported in 30–40% of COVID-19 survivors, similar to survivors of other pathogenic coronaviruses
- The pathophysiology of neuropsychiatric complications is mechanistically diverse and entails immune dysregulation, inflammation, microvascular thrombosis, iatrogenic effects of medications and psychosocial impacts of infection

Renal
- Resolution of AKI during acute COVID-19 occurs in the majority of patients; however, reduced eGFR has been reported at 6 months follow-up
- COVAN may be the predominant pattern of renal injury in individuals of African descent
- COVID-19 survivors with persistent impaired renal function may benefit from early and close follow-up in AKI survivor clinics

Endocrine
- Endocrine sequelae may include new or worsening control of existing diabetes mellitus, subacute thyroiditis and bone demineralization
- Patients with newly diagnosed diabetes in the absence of traditional risk factors for type 2 diabetes, suspected hypothalamic–pituitary–adrenal axis suppression or hyperthyroidism should undergo the appropriate laboratory testing and should be referred to endocrinology

Gastrointestinal and hepatobiliary
- Prolonged viral fecal shedding can occur in COVID-19 even after negative nasopharyngeal swab testing
- COVID-19 has the potential to alter the gut microbiome, including enrichment of opportunistic organisms and depletion of beneficial commensals

Dermatologic
- Hair loss is the predominant symptom and has been reported in approximately 20% of COVID-19 survivors

MIS-C
- Diagnostic criteria: <21 years old with fever, elevated inflammatory markers, multiple organ dysfunction, current or recent SARS-CoV-2 infection and exclusion of other plausible diagnoses
- Typically affects children >7 years and disproportionately of African, Afro-Caribbean or Hispanic origin
- Cardiovascular (coronary artery aneurysm) and neurologic (headache, encephalopathy, stroke and seizure) complications can occur

Ref 1 Ani Nalbandian Nat Med April 2021

Table 1. Long COVID-19 Syndrome on various systems: an evidence-based summary.

Systems	Main Diagnosis	Features	Possible Mechanisms	Prognosis	References
Respiratory system	Acute respiratory distress syndrome (ARDS)	Extensive bilateral diffuse alveolar damage with cellular fibromyxoid exudates; desquamation of pneumocytes and hyaline membrane formations; diffusion impairment and pulmonary fibrosis.	SARS-CoV-2 spike S1 domain protein binding to ACE2 receptor; Post Acute Respiratory Distress Syndrome fibrosis with diffuse alveolar damage	Pulmonary function deficit 6 months after infection; extensive diffuse impairment; Long-term in-situ thrombosis	[19–30]
Cardiovascular system	Endothelitis; Micro-thrombosis, Capillary damage; hypercoagulability; microangiopathy; thromboembolism; myocarditis; atrial fibrillation; supraventricular tachycardia	Increased target-to-blood pool ratio; capillary disturbance; impaired oxygen diffusion.	Cytokine storm and macrophage activating syndrome-caused endothelial dysfunction.	Majority (81%) of the COVID-19 myocarditis patients survived the acute episode; ongoing subclinical myocarditis may evolve into myocardial dysfunction and sudden cardiac death.	[31–35]
Haematological system	Thromboembolism	Elevated convalescent D-dimer and C-reactive protein levels; persistently increased biomarkers of inflammation.	N/A	Prognostic biomarkers for monitoring clinical progression of Long COVID-19 patients need to be investigated	[36–38]
Urinary system	Acute kidney injury; renal failure;	Declined glomerular filtration rate (eGFR); kidney infarction	High abundance pf ACE2 expression in kidneys.	Significant risks of mortality and morbidity	[39–42]
Digestive system	Gastrointestinal impairment and dysfunction; hepatitic and cholestatic liver injury; pancreatic injury	Bowel diffuse damage; Enterocytes desquamation, edema, small bowel dilation, lymphocytes infiltration and mesenteric nodes hemorrhage and necrosis.	Rich in ACE2 and furin expression; fecal-oral transmission; plasma cells and lymphocytic infiltrations into lamina propria of intestinal tissues.	The liver enzymes remained persistently elevated 14 days after discharge, while the liver functions in majority survivors normalized 2 months after hospital discharge	[43–49]
Neurological system	Mood changes; cognitive difficulties; headache; fatigue; dizziness; memory loss; confusion; and attention deficit.	Hypoxic injury; microbleedings; neuronal inflammations.	Blood vessel damage, impaired oxygen supply, viral infiltration into the central nervous system and inflammatory cytokines-mediated cellular damage; indirect T-cell and microglia damage in the brain, similar to strokes and neuroinflammatory diseases.	Over 40% survivors without prior psychiatric conditions lived with depression within 90 days of recovery from severe COVID-19 associated respiratory failure, while 70% of them did not receive treatment for depression	[50–55]
Metabolic system	Hyperglycaemia without diabetic mellitus; new-onset diabetic mellitus; starvation ketoacidosis	High blood glucose level; impaired glucose metabolism	Intruding pancreatic β-islet cells, triggering autoimmune responses because of the exposure of the antigen from damaged islet cells.	Long-term treatment of diabetic mellitus is needed.	[56–59]

Clinical evaluation and management of Long COVID

Table 1. Overall and time-specific incidence of long COVID symptoms

Symptom	Meta-analysis[a], % (95% CI)
Systemic	
Fever	1.1 (0.2 - 4.7)
Fatigue	31.0 (23.9 - 39.0)
Dizziness	4.5 (2.5 - 7.9)
Cardiopulmonary	
Cough	8.2 (4.9 - 13.4)
Sputum	5.5 (3.2 - 9.2)
Sore throat	4.7 (2.4 - 8.9)
Dyspnea	25.1 (17.9 - 34.0)
Chest pain/chest discomfort	6.4 (3.2 - 12.4)
Palpitation	9.7 (6.0 - 15.3)
Gastrointestinal	
Anorexia	17.5 (4.1 - 51.0)
Nausea/vomiting	6.7 (1.6 - 23.6)
Abdominal discomfort	18.0 (11.5 - 26.1)
Neurological	
Headache	4.9 (2.3 - 10.1)
Seizures/cramps	1.3 (0.5 - 2.9)
Taste disturbance	13.5 (9.0 - 19.9)
Smell disturbance	15.2 (10.8 - 21.0)
Tingling/paresthesia	9.1 (2.2 - 30.9)
Neurocognitive	
Concentration impairment	26.0 (21.0 - 31.7)
Memory impairment	17.9 (5.3 - 46.3)
Other cognitive impairment	17.8 (0.1 - 98.2)
Psychological	
Depression	8.1 (4.1 - 15.1)
Anxiety	18.7 (9.0 - 35.3)
Sleep disorder (insomnia)	18.2 (9.6 - 31.6)
Post-traumatic stress disorder	9.1 (3.7 - 21.0)
Musculoskeletal	
Muscle pain/myalgia	11.3 (6.2 - 19.8)
Joint pain/arthralgia	9.4 (5.7 - 15.0)
Other	
Hair loss	14.3 (5.3 - 33.2)
Skin rash	2.8 (1.0 - 8.2)

[a]Meta-analysis was conducted on a total of 10,951 patients with confi
countries, 12 weeks or more from the onset of symptoms.
COVID, coronavirus disease; CI, 95% confidence interval.

10/18/2022

Most common symptoms of long-COVID:

- 25 %: Fatigue –dyspnea – concentration impairment
- 10 % : Memory –anxiety – sleep disorder
  Anorexia – abdominal discomfort
  Taste and smell disturbance
  Hair loss
  Muscle weakness and joint pain

To be excluded as diseases that may develop after COVID, but are NOT long COVID

Table 2. Diseases that may develop after COVID-19

Classification	Systemic diseases
Circulatory system	Myocarditis, pericarditis, microvascular angina, cardiac arrhythmias (atrial flutter, atrial fibrillation), dysautonomia (postural orthostatic tachycardia syndrome)
Respiratory system	Interstitial lung disease, pulmonary emboli
Gastrointestinal system	Hepatitis, abnormal liver enzymes, pancreatitis
Endocrine system	New-onset diabetes (diabetic ketoacidosis, *etc.*), thyroiditis (subacute thyroiditis, Graves' disease, Hashimoto thyroiditis, *etc.*), adrenal insufficiency
Neurological system	Cerebral venous thrombosis, myelopathy, neuropathy, neurocognitive disorders, dysphonia, encephalitis, Guillain-Barré syndrome
Musculoskeletal system	Arthritis, myositis
Other	Renal impairment (tubulopathies, glomerulonephritis)
	Autoimmune diseases (systemic lupus erythematosus, vasculitis, sarcoidosis)
	Mast cell activation syndrome
	New-onset allergies/anaphylaxis
	Perniosis

Ref 6 Yoonjung Kim Infect Chemother. 2022 Sep;54(3):566-597

Clinical evaluation and management of Long COVID

What TESTS for Long COVID?

1) **Dyspnee:** pulmonary function tests (including diffusion capacity); X-ray after 3 months, CT if doubt.
2) **Cough:** If > 3 months: X-ray and CT: exclude pulmonary parenchymal fibrosis or bronchial inflammation
3) **Chest pain:** Transthoracic echocardiography: pericarditis or myocarditis?
   Functional tests such as the 6-minute walking test to evaluate cardio-pulmonary function
4) **Fatigue**: vide infra

5) **Joint or muscle pain**: laboratory tests for exclusion: (creatine kinase, lactate dehydrogenase, C-reactive protein, rheumatologic factor, anti-nuclear antibody)
6) **Headache**: neurological examination. If suspicious: brain imaging

7) **Cognitive or psychological/mental symptoms** : neuro-psychological examination. If suspicious: brain imaging

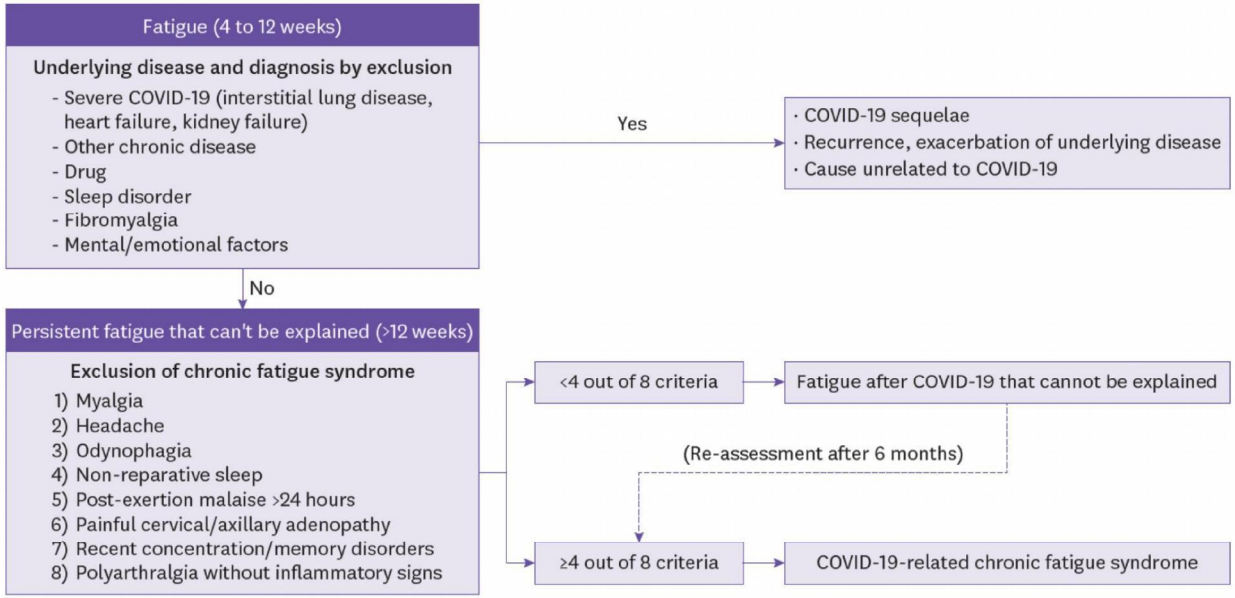
Laboratory tests? No specific test. Mainly for exclusion:

- General: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complete blood count (CBC), and liver function test (LFT).
- Heart-related problems: myocardial enzyme tests (troponin, creatine kinase-myoglobin binding [CK-MB]) and brain natriuretic peptide tests (B-type natriuretic peptide BNP).
- Dyspnee: arterial O2 saturation
- Endocrine: thyroid function; fasting glucose and (if suspect) glycosylated Hemoglobin.

Ref 6 Yoonjung Kim Infect Chemother. 2022 Sep;54(3):566-597

Clinical evaluation and management of Long COVID

Distinguish fatigue due to long COVID from other causes



Ref 6 Yoonjung Kim Infect Chemother. 2022 Sep;54(3):566-597

The LONG COVID CONUNDRUM

1) Definition, scope and classification

2) Risk factors

3) Pathophysiology

4) Management

Post-COVID Conditions US March 2020-NoV 2021 according to age

TABLE. Percentage of adult COVID-19 case-patients and control patients with ≥1 post-COVID–attributable incident conditions and estimated number of COVID-19 survivors who will experience a post-COVID condition — United States, March 2020–November 2021

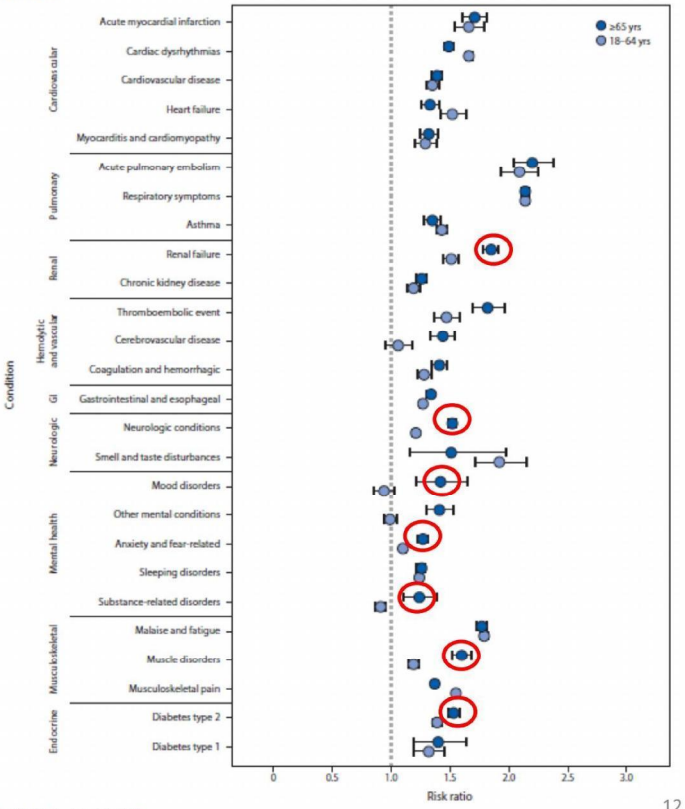
Age group, yrs	No. of patients (column %) Case-patients	Control patients	No. of patients with ≥1 incident condition (column %*) Case-patients	Control patients	Absolute risk difference†	No. of COVID-19 survivors with a post-COVID condition§
18–64	254,345 (72.0)	1,051,588 (64.1)	90,111 (35.4)	154,011 (14.6)	20.8	1/5
≥65	98,819 (28.0)	589,188 (35.9)	44,840 (45.4)	108,850 (18.5)	26.9	1/4
Total	**353,164 (100)**	**1,640,776 (100)**	**134,951 (38.2)**	**262,861 (16.0)**	**22.2**	**1/4–5**

* Percentage of COVID-19 case-patients or control patients with ≥1 incident condition divided by the total study COVID-19 cohort or control cohort row's age group total.
† Percentage point difference between COVID-19 case-patients and control patients (e.g., the value 20.8 is calculated as 35.4 minus 14.6).
§ Number of COVID-19 survivors who experienced a post-COVID condition estimated as the inverse of the absolute risk difference.

Compare incidence of 26 conditions often attributable to post-COVID
- Cases = patients with a previous COVID-19 diagnosis
- Controls = matched patients without evidence of COVID-19

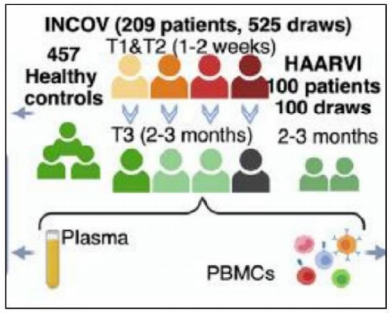
Older people higher risk, especially for renal failure, neurological and mental health problems, muscle disorders and type 2 diabetes

FIGURE. Risk ratios* for developing post-COVID conditions among adults aged 18–64 years and ≥65 years — United States, March 2020–November 2021



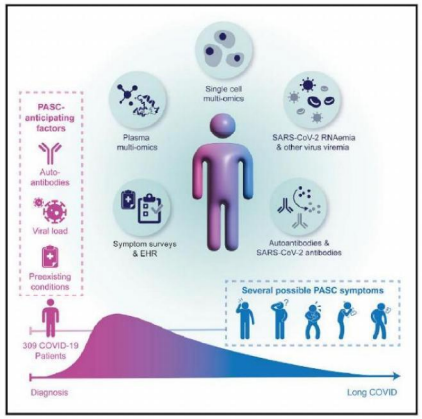
Abbreviation: GI = gastrointestinal.
* With CIs indicated by error bars; some error bars are not visible because of small CIs.

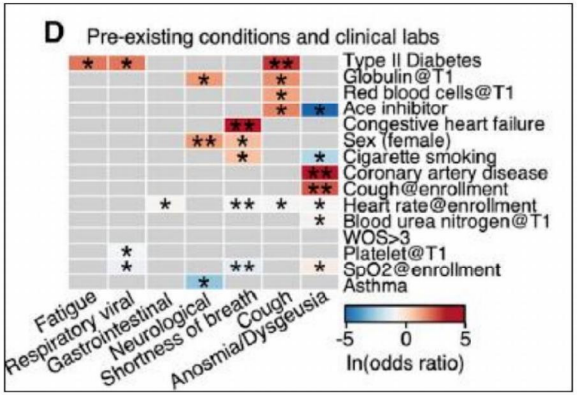
Multiple early factors anticipate post-acute COVID-19 sequelae



INCOV cohort with
- 457 healthy controls
- 100 Post-Acute COVID-19 patients =PACS or HAARVI

Blood drawn at T1-T2 (week 1 and 2 = acute phase)
T3 = 2-3 months





<u>Pre-existing conditions, favoring particular long-COVID symptoms</u>:
- Type 2 diabetes → fatigue, respiratory viral; cough
- High immunoglobin or RBC at T1 → cough
- Female sex → neurological
- Congestive heart failure → shortness of breath
- Coronary heart disease or cough at T1 → anosmia/ageusia
- …

Ref 8 Yapeng Su Cell (2022) vol 185 p 881

Established Risk factors for long COVID:

Older age,

Non-white ethnicity,

Disabled,

Pre-existing **comorbidities** including obesity, diabetes , respiratory/ cardiovascular disease and hypertension

Male sex (?)

Immune suppression ?

Seveity of COVID?

Other risk factors?

Variant?

Successive infections?

Vaccination?

Children?

Long COVID during Omicron in UK

Case control in UK adults on
- 41 361 first testing positive during **Delta** period
- 56 003 first testing positive during **Omicron BA.1/2** period

How many new or ongoing symptoms 4 weeks or more after the start of acute COVID-19 ?

Comparison % long-COVID after delta and omicron according to age and time since vaccination (2 doses)

		18-59	> 60 yrs
Time since vacc	SARS-CoV-2 VOC		
> 6 mo	Delta	9.7	14.7
	Omicron	2.1	4.2
3-6 mo	Delta	11.4	13.8
	Omicron	3.7	5.4
< 3 mo	Delta	6.6	10.4
	Omicron	4.0	5.2

Conclusion: Omicron has lower risk on long-COVID, but the absolute numbers may eventually become higher
(No clear relation with time since vaccination)

Ref 10 Anil Dhawan Lancet 18 June 2022

Prevalence of SARS-CoV-2 and long COVID in US adults during the BA.5 surge, June-July 2022

Survey amongst 3,042 US adults:

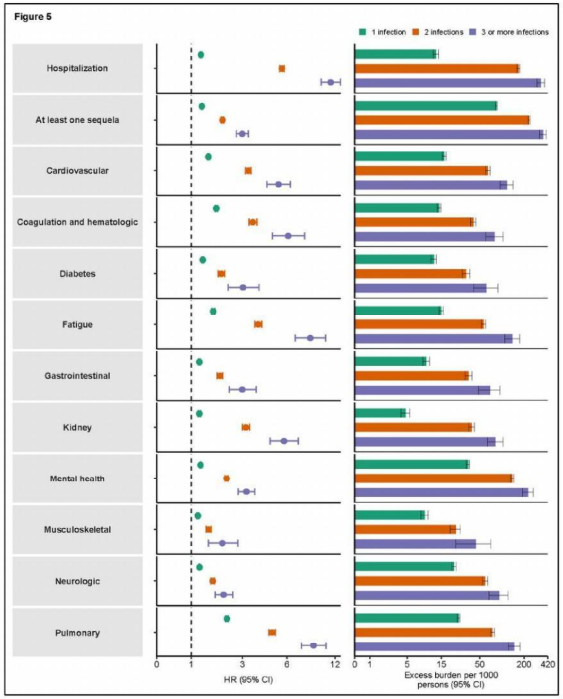
- 17.3% reported SARS-CoV-2 infection during 2 preceding weeks

- **21.5%** of respondents with a SARS-CoV-2 infection more than 4 weeks prior reported **long COVID** symptoms
  - More in **women**: RR 1.8 (1.4-2.3).
  - More in people with **co-morbidities**: RR 1.8 (1.4-2.3).
  - More if **health insurance**: RR 1.9 (1.3, 2.7)
  - No clear-cut association with age, but slightly **lower in 65**+ RR 0.7 (0.5 -1.1)
  - Tends to be more with **lower income**.

Obviously a very limited study

Ref 11 Saba Qasmieh medRxiv 6 Sept 2022

Risk of long COVID increases with each infection



With **each reinfection** increase the chances of **complications AFTER recovery**, including premature death (based on large cohort of US Veterans Administration).

Ref 9 5.1.2e 21 June 2022

Effect of vaccination on long COVID

Table 2. Results of the subgroup analysis of the effect of vaccination on long COVID.

Subgroups	The Number of Studies	The Number of People	I^2 (%)	RR (95% CI)	*p* Value of Meta-analysis
The number of vaccine doses					
1 dose	6	655,962	99	0.83 (0.65–1.07)	0.14
2 doses	7	420,402	90	0.83 (0.74–0.94)	<0.01
Age					
<60 years	3	12,415	89	0.76 (0.54–1.06)	0.11
≥60 years	2	9509	55	0.87 (0.60–1.24)	0.43
Vaccination time					
Before SARS-CoV-2 infection/COVID-19	6	180,996	97	0.82 (0.74–0.91)	<0.01
After SARS-CoV-2 infection/COVID-19	4	2508	24	0.83 (0.74–0.92)	<0.01
Definition of long COVID					
Presence of symptoms more than 4 weeks after SARS-CoV-2 infection/COVID-19 diagnisis *	7	419,374	87	0.68 (0.53–0.87)	<0.01
Other definitions	8	526,302	99	0.75 (0.64–0.88)	<0.01

Ref 12 Peng Gao Int. J. Environ. Res. Public Health **2022**, 19, 12422

Effect of vaccination on long COVID

Table 3. Effects of vaccination on long COVID symptoms.

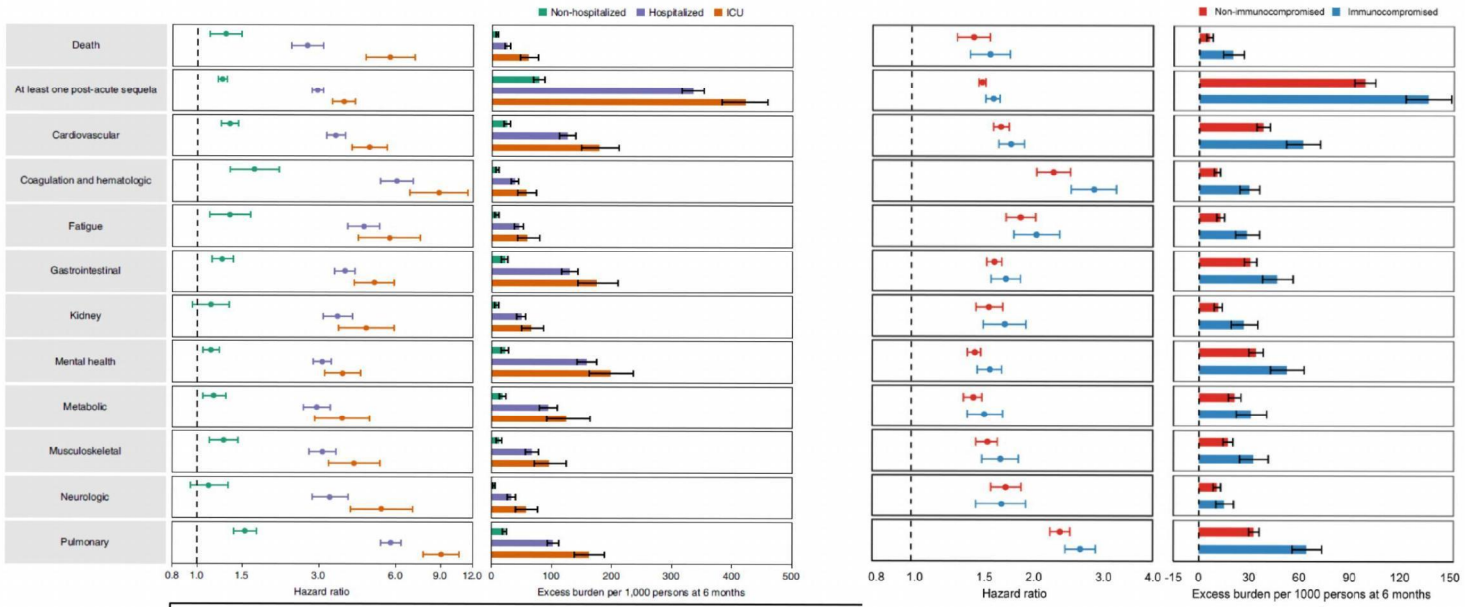
Long COVID Symptom	The Number of Studies	The number of People	I^2 (%)	RR (95% CI)	*p* Value of Meta-Analysis
Anxiety and/or depression	4	28,604	70	0.83 (0.67–1.03)	0.08
Chest or throat pain	3	26,386	0	1.01 (0.95–1.08)	0.67
Cognitive dysfunction/symptoms	2	22,124	8	0.89 (0.83–0.96)	<0.01
Fatigue	6	225,478	97	0.77 (0.58–1.02)	0.07
Hair loss	2	6480	50	0.86 (0.62–1.19)	0.37
Headache/migraine	4	76,836	99	0.95 (0.50–1.79)	0.87
Kidney diseases/problems	2	148,365	0	0.68 (0.64–0.73)	<0.01
Loss of concentration	2	6480	71	0.65 (0.35–1.19)	0.16
Loss of smell	3	8698	75	0.67 (0.36–1.26)	0.21
Loss of taste	3	8698	68	0.71 (0.48–1.07)	0.10
Myalgia	2	25,435	15	0.68 (0.62–0.74)	<0.01
Nausea and/or vomiting	2	6480	87	0.80 (0.31–2.02)	0.63
Respiratory symptoms/sequelae	5	78,064	98	0.91 (0.60–1.40)	0.68
Sleeping disorders/problem sleeping	3	8698	25	0.74 (0.64–0.86)	<0.01
Weight loss	2	6480	95	1.24 (0.22–7.05)	0.81

Conclusion: 2 doses of vaccination, either before or after infection, lower the risk on long COVID with 20-25 %, especially with regard to cognitive and sleeping disorders as well as kidney problems and myalgia

Ref 12 Peng Gao Int. J. Environ. Res. Public Health **2022**, 19, 12422

Long COVID after SARS-CoV-2 breakthrough infection (BTI)

(based on large cohort of US Veterans Administration)



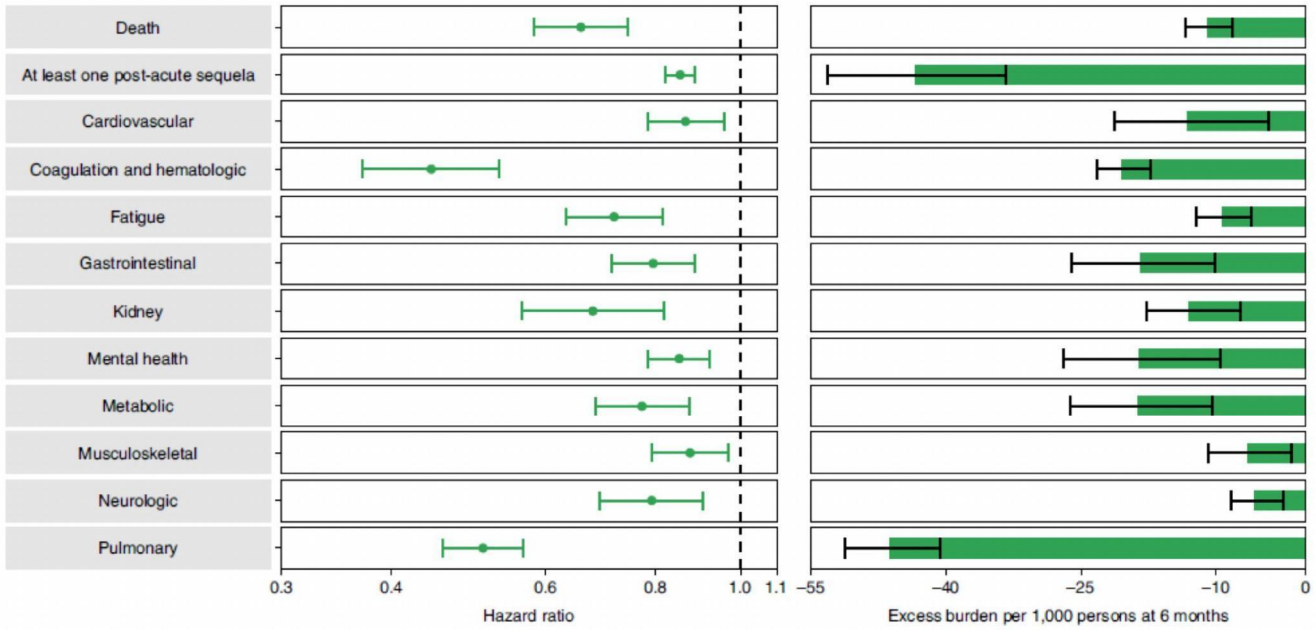
Relative risk and excess burden of each long-COVID symptom in breakthrough after vaccination is higher

- for ICU > hospitalized > ambulatory patients (left panel)
- for immunocompromised (right panel)

Ref 13 Ziyad Al Ali Nat Med 22 May 2022

Long COVID after SARS-CoV-2 breakthrough infection (BTI)

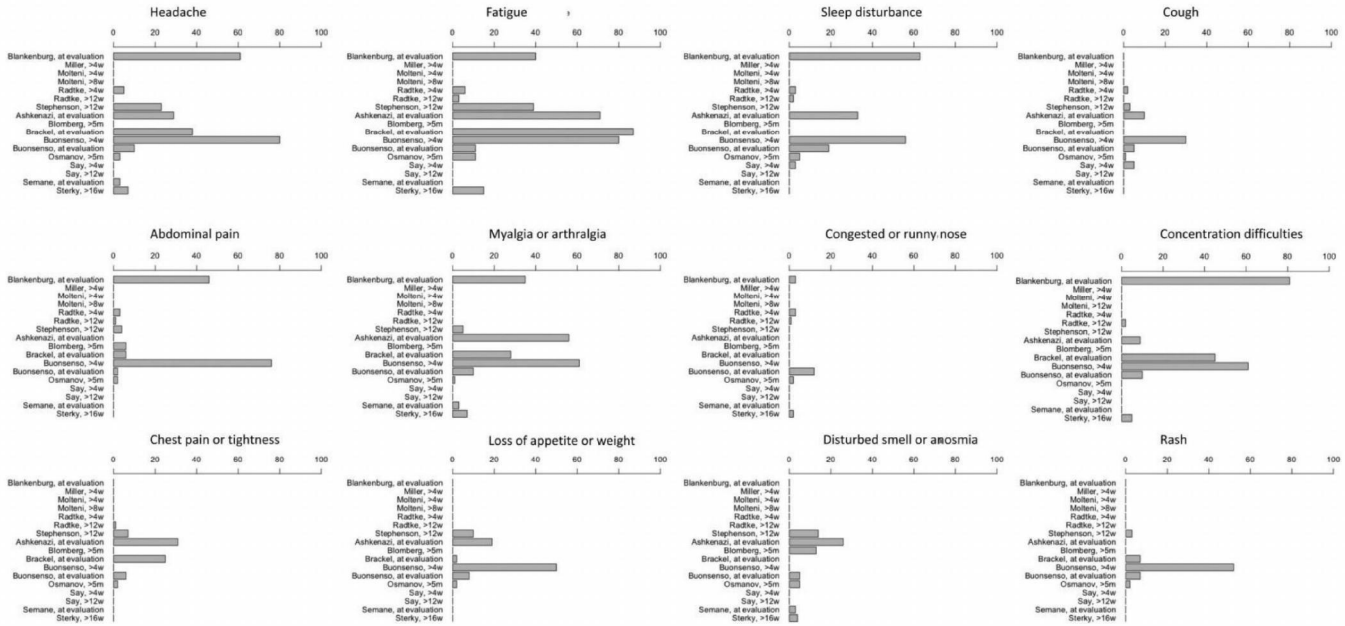
(based on large cohort of US Veterans Administration)



Nevertheless risk and excess burden of long-COVID in BTI (after vaccination) is in general lower as in those without prior vaccination

Ref 13 Ziyad Al Ali Nat Med 22 May 2022

How Common is Long COVID in Children and Adolescents?

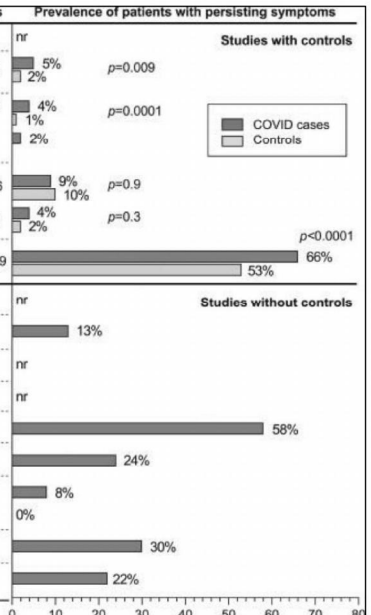


As in adults, a wide range of persistent symptoms has been reported with widely different frequencies

Petra Zimmermann J Pediatric Infect Dis Dec 2021

How Common is Long COVID in Children and Adolescents?

First author	Country	Study	Age (y)[a]	Timing	Cases	Controls
Blankenburg	Germany	CS	median 15 (14-16)	nr	nr	nr
Miller	UK	PCS	nr, ≤17	4w	8/174	72/4504
Molteni	UK	PCS	median 13 (10-15)	4w	77/1734	15/1734
				8w	25/1734	nr
Radtke	Switzerland	PCS	median 11 (nr)	4w	10/109	121/1246
				12w	4/109	28/1246
Stephenson	UK	PCS	range 11-17	12w	2038/3065	1993/3739
Ashkenazi-Hoffnung	Israel	PCS	mean 12 (5)	[b]	90	-
Blomberg	Norway	PCS	median 8 (6-12)	5m	2/16	-
Brackel	Netherlands	CS	median 13 (9-15)	nr	89	-
Buonsenso	UK, USA	CS	mean 10 (3.8)	4w	510	-
Buonsenso	Italy	CS	mean 11 (4.4)	[c]	75/129	-
Osmanov	Russia	PCS	median 10 (3-15)	5m	126/518	-
Say	Australia	PCS	mean 3.7 (3.5)	4w	12/151	-
				12w	0/151	-
Smane	Latvia	RCS	mean 9.2 (5.2)	[d]	9/30	-
Sterky	Sweden	PCS	nr, ≤18	16w	12/55	-



[a] mean (SD), median (interquartile range), or range;
[b] median 112d after infection, range 33-410d
[c] mean 163d after infection, SD 114d
[d] mean 101d after infection, SD 17d

CS, cross-sectional study; d, days; m, month; nr, not reported; PCS, prospective cohort study; RCS, retrospective cohort study; SD, standard deviation; w, weeks; y, years

Only in 2 out of 5 controlled studies prevalence of persistent symptoms was higher post-COVID

Petra Zimmerman Pediatric Infect Dis Dec 2021

No difference of persistent symptoms following SARS-CoV-2 infection amongst children and young people in controlled studies

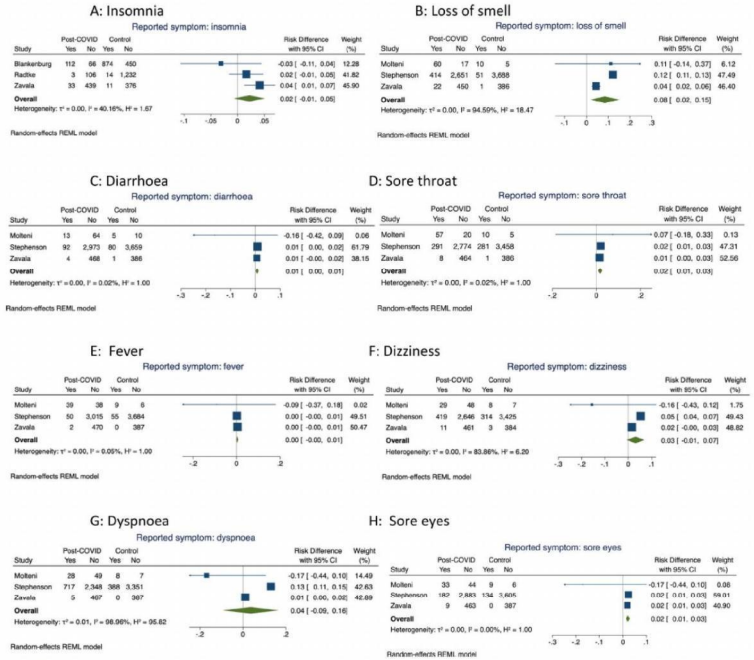


Fig. 3. Meta-analyses of risk difference in symptom prevalence between cases and control participants in controlled studies: analyses including symptoms reported in 3 or more studies.

Ref 26 S.A. Behnood J Infect 2022 84 158-170

Established Risk factors for long COVID:

Older age,

Non-white ethnicity,

Disabled;

Pre-existing **comorbidities** including obesity, diabetes , respiratory/ cardiovascular disease and hypertension

Male sex (?)

Immune suppression: yes

ICU > hospitalized > ambulatory

Other risk factors?

Variant: omicron proportionally less long COVID

Successive infections: progressive increase in prevalence of long COVID

Vaccination: partial protection.

Children: less long COVID?

The LONG COVID CONUNDRUM

1) Definition, scope and classification

2) Risk factors

3) **Pathophysiology:** hypotheses and associations

4) Management

Pathophysiology hypotheses and associations:

- **General**
- Pulmonary
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- Kidney

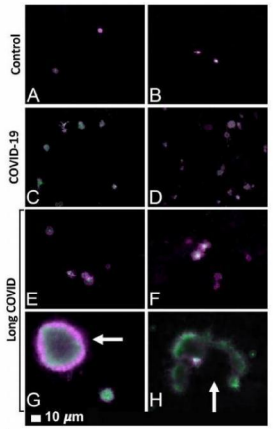
Three major pathogenic hypotheses for long-COVID

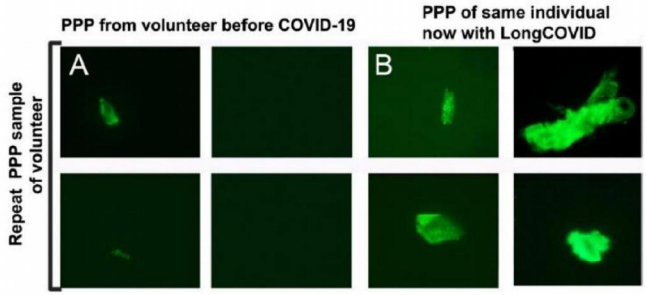
1) Microclots? generated by coagulopathy during acute phase, could obstruct small vessels in
- Lungs → respiratory complaints;
- Brain → "fog" and fatigue;
- Dysregulating autonomous nerves: disrupt heart rate, breathing, and digestive function.

2) Persistent virus ?

3) Immune system in constant high alert and low cortisol

Jennifer Couzin-Frankel Science 16 June 2022

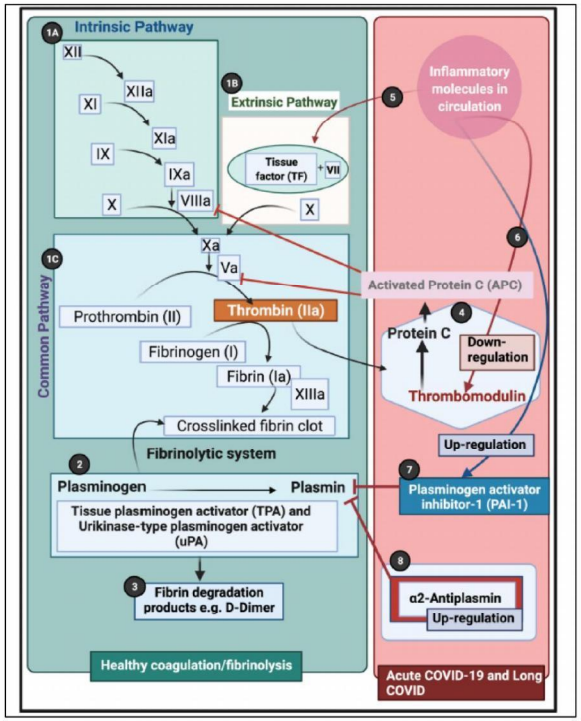




Large microclot aggregates in platelet poor plasma (PPP) from long-COVID

Ref 15 Pretorius. Cardiovasc Diabetol (2021) 20:172

Persistent clotting protein pathology in Long COVID is accompanied by increased antiplasmin



(1A) The intrinsic and (1B) extrinsic pathways converge into the (1C) common pathway. These pathways lead to the conversion of soluble fibrinogen to insoluble fibrin, catalysed by thrombin.

(2) Tissue plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA) converts plasminogen into plasmin. A healthy fibrinolytic system regulates the coagulation pathway and assists with successful lysis of the insoluble fibrin clot.

(3) Plasmin cleaves fibrin into fibrin degradation products (FDPs), including D-dimer.

(4) Protein C and thrombomodulin both regulate coagulation: thrombin binds to its receptor, thrombomodulin, resulting in activated protein C (APC). APC then inhibits both Va and VIIIa.

Effect of dysregulated inflammatory molecules

(5) may **interfere with tissue factor** (TF) expression.

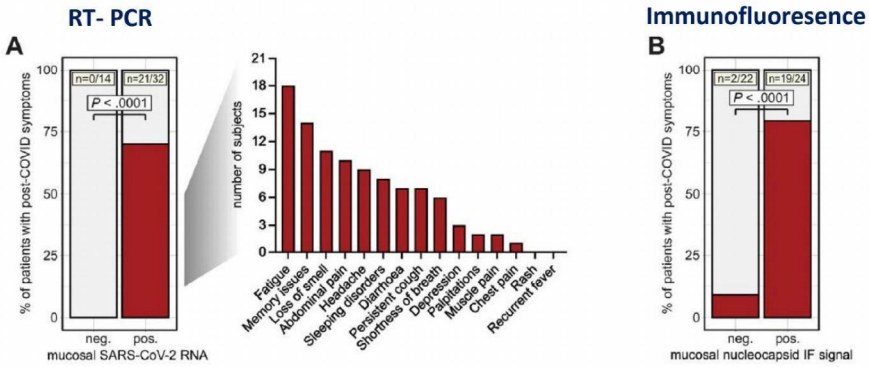
(6) may also **down-regulate thrombomodulin**, resulting in hypercoagulation, as Va and VIIIa activities are then not sufficiently modulated.

(7) can **inhibit of the fibrinolytic system** via up-regulation of plasminogen activator inhibitor-1 (PAI-1). PAI-I upregulation interferes with tissue plasminogen activator (TPA) function, and ultimately results in a dysregulated coagulation system.

(8) **α2-antiplasmin (α2AP) inhibits plasmin** and will prevent sufficient fibrinolysis

Ref 15 Pretorius. Cardiovasc Diabetol (2021) 20:172

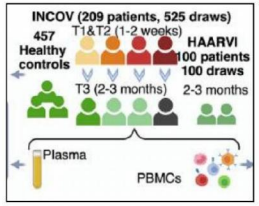
Long COVID is characterized by gut SARS-CoV-2 persistence in Inflammatory Bowel Diseases



Presence of various long-COVID symptoms is associated with viral persistence (PCR and immunofluorescence) in 46 patients with inflammatory bowel disease (IBD) 219 days (range, 94–257) after a confirmed COVID-19 infection

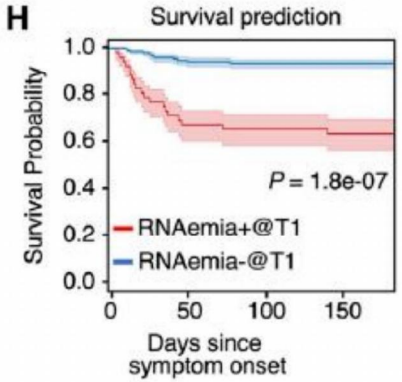
Ref 16 Andreas Zollner Gastro-Enterology May 2022

Early presence of SARS-CoV-2 and EBV in plasma anticipates poor survival and post-acute COVID-19 sequelae

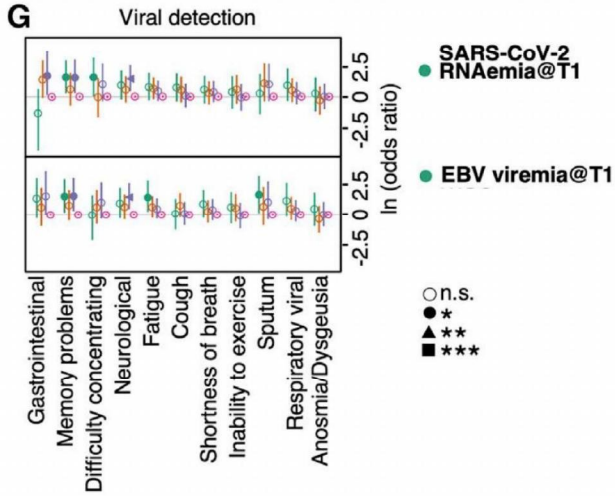


INCOV cohort with
- 457 healthy controls
- 100 Post-Acute COVID-19 patients

Blood drawn at T1 = (week 1 = acute phase)



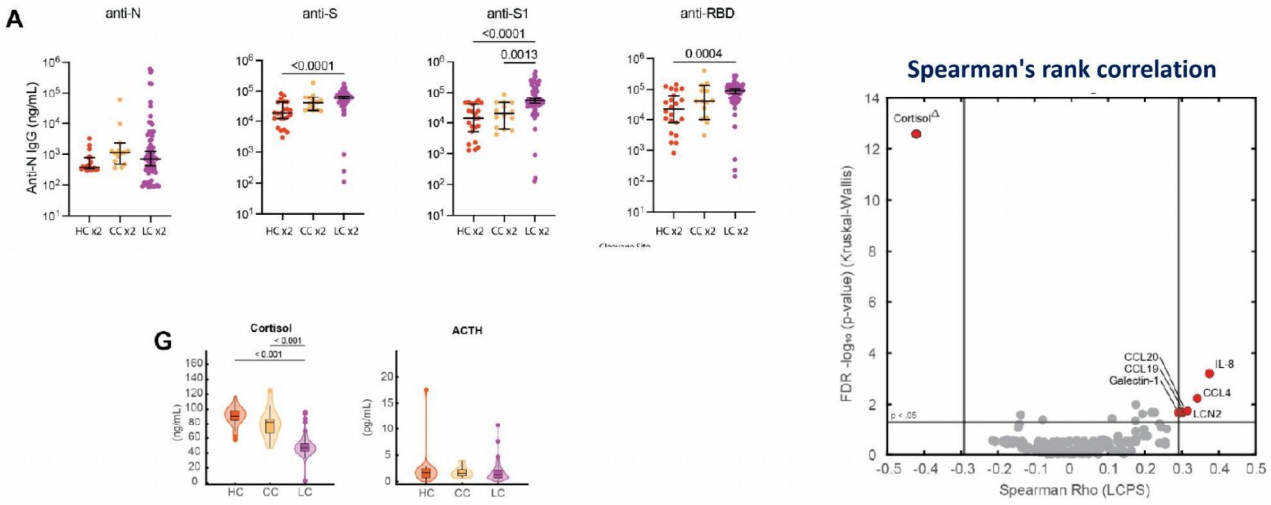
Patients with SARS-CoV-2 viremia at T1 survive less



High viremia (SARS-CoV-2 or EBV) at T1 predisposes to long-COVID

Ref 8 Yapeng Su Cell (2022) vol 185 p 881

Distinguishing features of Long COVID identified through immune profiling

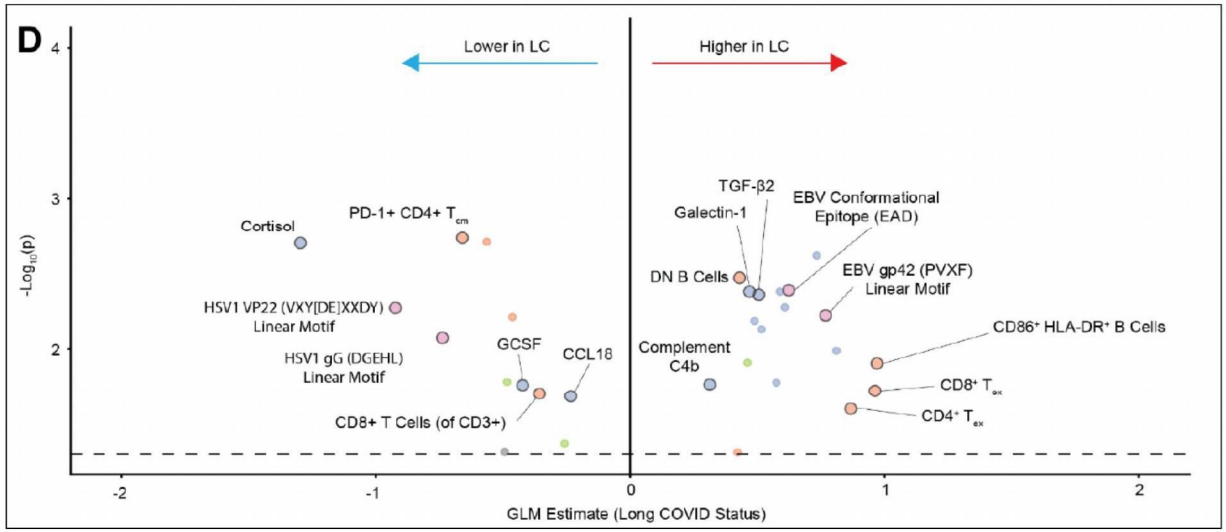


Long-COVID: higher levels of antibodies to SARS-CoV-2 Spike = **persistence of SARS-CoV-2?**
very **low levels of cortisol and ACTH**
associated with low cortisol and high IL-8, CCL4, CCL19, CCL20, Galectin-1 = **inflammation?**

Ref 17 Jon Klein medRxiv 10 August 2022

Distinguishing features of Long COVID (LC) identified through immune profiling

LASSO = regression analysis with high predictive value



Long-COVID: higher levels of	some soluble factors: TGF-β2, Galectin-1, Complement C4b = **inflammation** some lymphocyte subsets e.g. **exhausted** CD4+ and CD8+ T cells; **activated** B cells (CD86, HLA-DR+) antibodies to EBV epitopes: **reactivation?**
low levels of cortisol	

Ref 17 Jon Klein medRxiv 10 August 2022

Pathophysiology hypotheses and associations:

- General
- **Pulmonary**
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- Kidney

What Are the Major Long-term Pulmonary Sequelae in Survivors of Critical COVID-19?

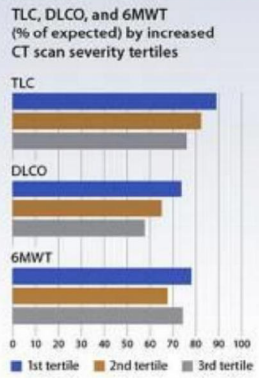
STUDY DESIGN

- Descriptive observational ICU survivor cohort of 62 adult patients with diagnosis of SARS-CoV-2 and ARDS in two Spanish hospitals between March and June 2020
- All needed at least HFNC during ICU stay and 62.9% were intubated
- At follow-up, assessed quality of life, performed CT scan of chest, and measured pulmonary function tests (TLC and DLCO), and 6-minute walk test (6MWT)

RESULTS

Three months after hospital discharge:

- An abnormal CT scan was seen in **70.2%** of patients, with fibrosis seen in **21.1%**
- Patients had a 6MWT distance of **128m less** than the healthy population (25-75% IQR -185.03; -62.66)
- **81.9%** of patients had DLCO impairment
- **15.2%** had altered depression scores and **22.1%** altered anxiety scores



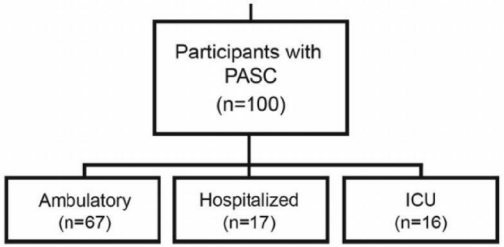
In survivors hospitalized in the ICU with COVID-19 and ARDS, lung involvement at 3 months post-discharge remained significant.

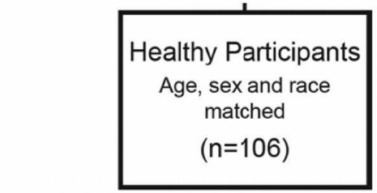
González Gutiérrez J, et al. *CHEST* July 2021
@journal_CHEST | https://doi.org/10.1016/j.chest.2021.02.062

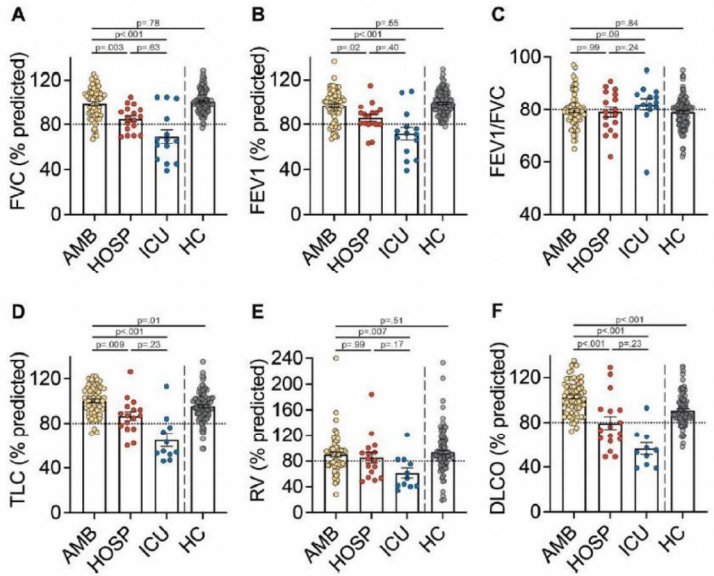
CHEST

Abbreviations: ICU = intensive care unit; HFNC = high flow nasal canule (with oxygen); CT = computerized tomography; TLC = Total Lung Capacity; DLCO = diffusion capacity; 6MWT = six minutes walking test

Air-trapping is a common feature of long COVID (PACS) independent of disease severity





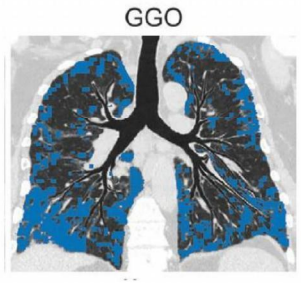


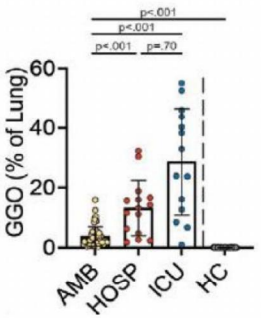
PACS with a history of ICU selectively show a deficit in several lung function tests

Abbreviations: FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, TLC = total lung capacity, RV = residual volume, Dlco = diffusing capacity of the lung for carbon monoxide; ICU = intensive care unit

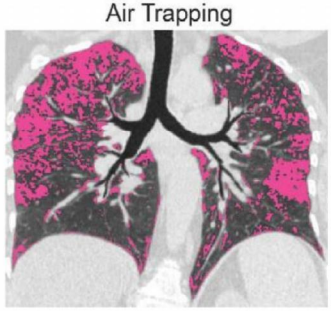
Ref 18 Josalyn Cho Radiology July 2022

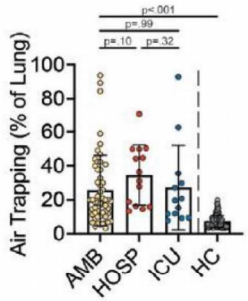
Air-trapping is a common feature of long COVID (PACS) independent of disease severity





Ground-glass opacities (GGO)
ICU > hospitalized >> ambulatory PACS >> healthy

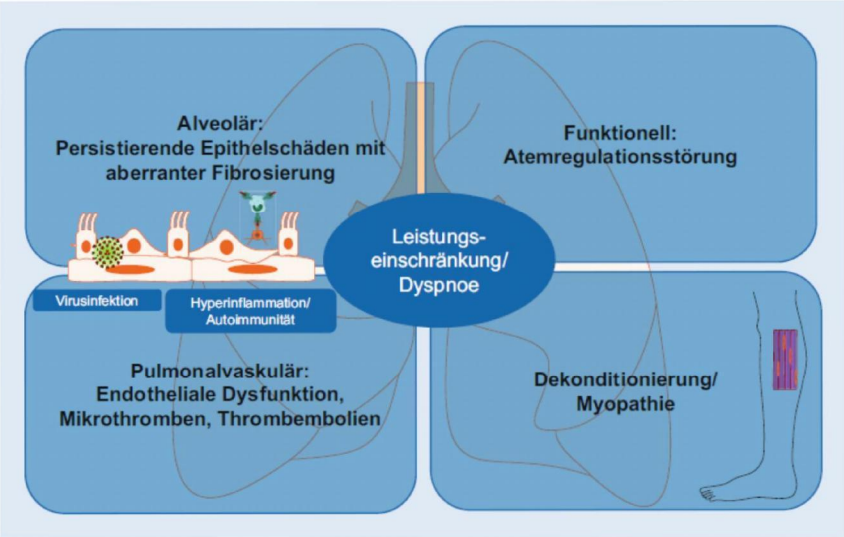


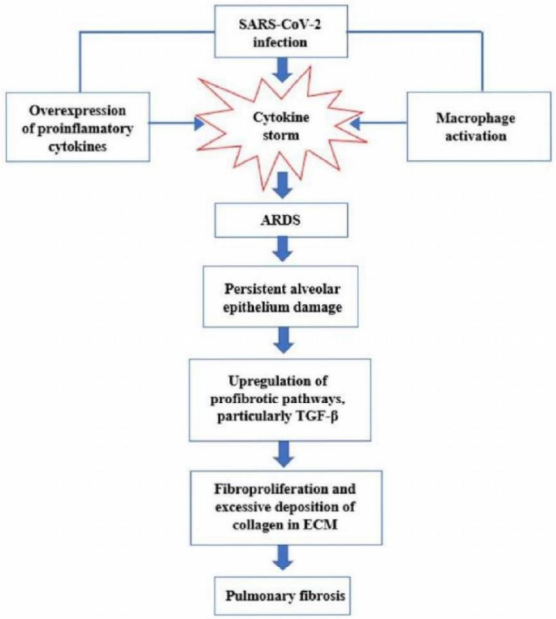


Air-trapping is common in all PACS
Could explain dyspnea, even if
classical lung function tests normal?

Ref 18 Josalyn Cho Radiology July 2022

Pulmonary (non cardiac) mechanisms in long-COVD dyspnea



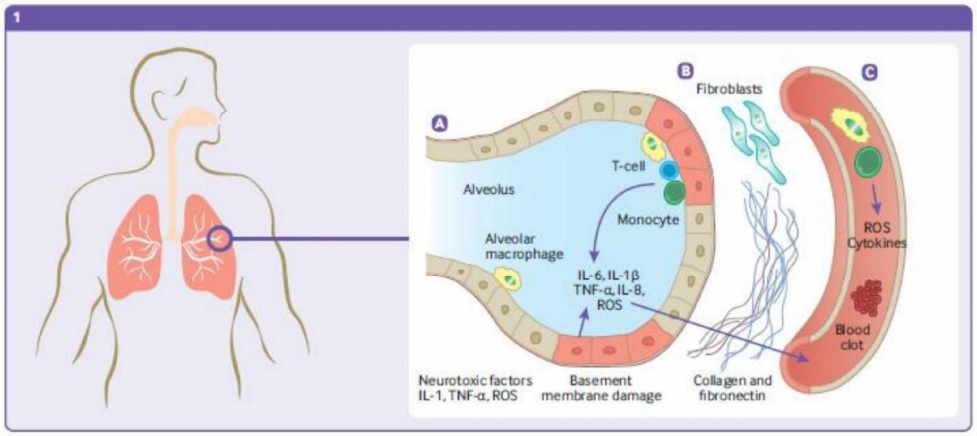


Note: Leistungs- einschränkung = exercise-limiting

Natascha Sommer Innere Medizin (2022) vol 63 p 819

Ref 4 Valentina Ruggiero Pharmaceutics 2022 vol 14 p 1135

Long term sequalae of covid-19 in the alveoli of the lungs



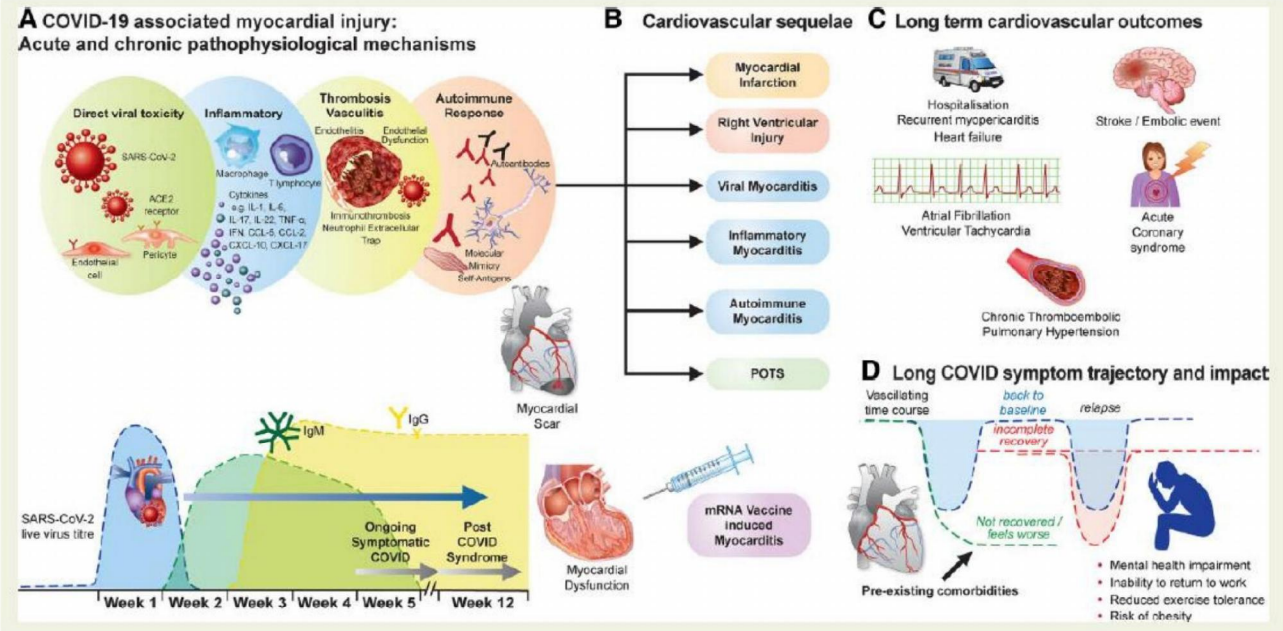
(A) **Pro-inflammatory cytokines and reactive oxygen species** (ROS) released into the tissue and bloodstream.
(B) **Endothelial damage** triggers fibroblasts, in fibrotic changes.
(C) Endothelial injury, complement activation, platelet activation, and platelet-leukocyte interactions, release of pro-inflammatory cytokines, disruption of normal coagulant pathways, and hypoxia may result in the development of a **prolonged hyperinflammatory and hypercoagulable state**, increasing the risk of thrombosis.

Harry Crook BMJ 2021;374:n1648

Pathophysiology hypotheses and associations:

- General
- Pulmonary
- **Cardiovascular**
- Anosmia (ageusia)
- Neurological
- Kidney

Long COVID with a cardiovascular focus



Note: ACE2, angiotensin-converting enzyme 2; CCL, chemokine ligand; COVID, coronavirus disease; IL, interleukin; IFN, interferon; Ig, immunoglobulin; PCR, polymerase chain reaction; POTS, postural orthostatic tachycardia syndrome; RNA, ribonucleic acid; TNF, tumour necrosis factor.

Ref 19 Raman Eur Heart J Oct 2022 vol 43 p. 1157

Long COVID with a cardiovascular focus

Table 1 Prevalence of cardiac abnormalities in studies ($n > 50$) that utilized echocardiography, cardiac magnetic resonance, and cardiopulmonary exercise test during follow-up of COVID-19 patients

First author	No. of patients	Age	Patient characteristics	Follow-up time	Controls	Cardiopulmonary symptoms	Echo findings
Echocardiography							
Hall *et al.*[135]	200	55 ± 15 years; 62% male	Hospitalized patients; 27.5% mechanical ventilation	4–6 weeks post-discharge	–	18% new-onset/worsening of dypsnoea	14% had either newly diagnosed or previously present abnormalities
Sechi *et al.*[130]	105	57 ± 14 years; 53% male	Hospitalized; 26% mechanical ventilation	Median 41 days post-symptom onset	105 matched controls	5% chest pain, 5% dyspnoea, 7% fatigue	No cardiac abnormalities
CMR CMR, cardiac magnetic resonance; C							
Kotecha *et al.*[101]	148	64 ± 12 years; 70% male	Severe COVID-19 and elevated troponin; 32% mechanically ventilated	Median 68 days post-discharge or confirmed diagnosis	40 co-morbidity matched and 40 healthy	No symptoms	11% LV dysfunction, 26% myocarditis, 23% ischaemia/ infarction, 6% had dual pathology
Puntmann *et al.*[122]	100	49 ± 14 years; 53% male	67% non-hospitalized	Median 71 days post-positive COVID-19 test	50 healthy and 57 co-morbidity matched controls	36% breathlessness, 17% chest pain, 20% palpitations	60% myocardial inflammation, 78% any abnormality including LV, RV dysfunction, late gadolinium enhancement, and pericardial enhancement
CPET CPET, cardiopulmonary exercise test;							
Clavario *et al.*[102]	110	62 (54–69 years); 59% male	Hospitalized (excluded pts requiring mechanical ventilation/ ICU)	3 months post-hospital discharge	–	74% at least one symptom. 50% dyspnoea, 26% chest pain, 49% fatigue, 23% palpitations	Median predicted pVO_2 90.9 (79.2–109). 35% had $pVO_2 < 80\%$ predicted. DLE maximal strength independently associated with pVO_2. 24% had cardiac limitation to exercise, 8% respiratory and cardiac, 47% non-cardiopulmonary limitation
Raman *et al.*[120]	58	55 ± 13 years; 59% male	Hospitalized patients at 3 months from symptom onset	3 months from symptom onset	30 co-morbidity matched controls	83% had at least one cardiopulmonary symptom	55% had $pVO_2 < 80\%$ predicted, VE/VCO_2 slope 33.[29–40] HRR in first minute was slower in patients compared with controls

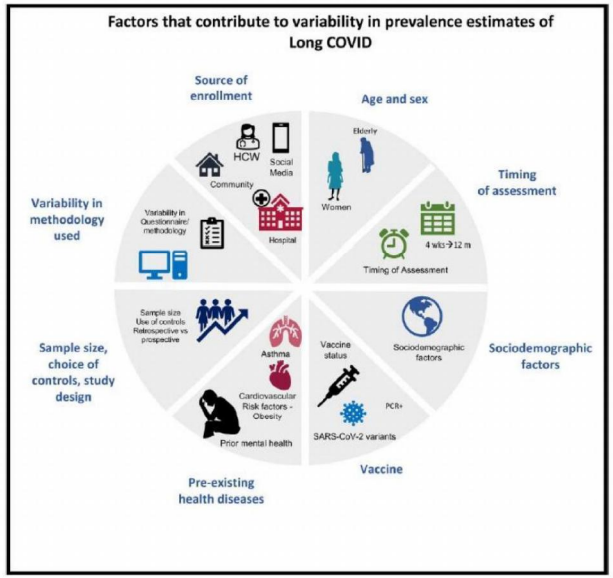
Data are presented as mean ± standard deviation or median (interquartile range).
AT, anaerobic threshold; BMI, body mass index; COVID, coronavirus disease; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; DLco, carbon monoxide gas transfer; GLS, global longitudinal strain; HRR, heart rate recovery; ICU, intensive care unit; LV, left ventricle; PCR, polymerase chain reaction; pVO_2, peak oxygen consumption; RV, right ventricle; PAP, pulmonary artery pressure; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VE/VCO_2, slope ventilatory equivalent for carbon dioxide; WR, work rate.

Variable results of objective cardiological findings after discharge from hospital

Ref 19 Raman Eur Heart J Oct 2022 vol 43 p. 1157

Long COVID with a cardiovascular focus

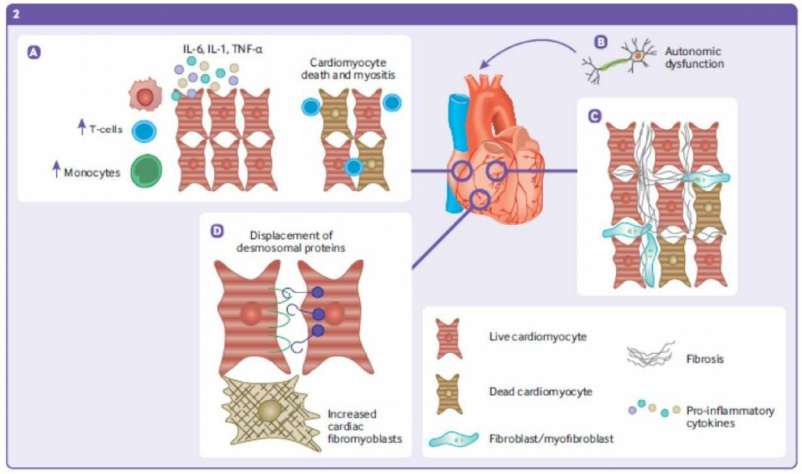
Modulating **factors,** determining to **variability of long COVID**



Differences in cohort characteristics, age, and sex of subjects enrolled, timing of assessment, sociodemographic factors, vaccines and variants, pre-existing health problems, sample size, study design, and variability in questionnaires or tools used.
HCW, healthcare workers; m, months; PCR, polymerase chain reaction; wks, weeks.

Raman Eur Heart J Oct 2022 vol 43 p. 1157

Long term sequalae of covid-19 in the heart



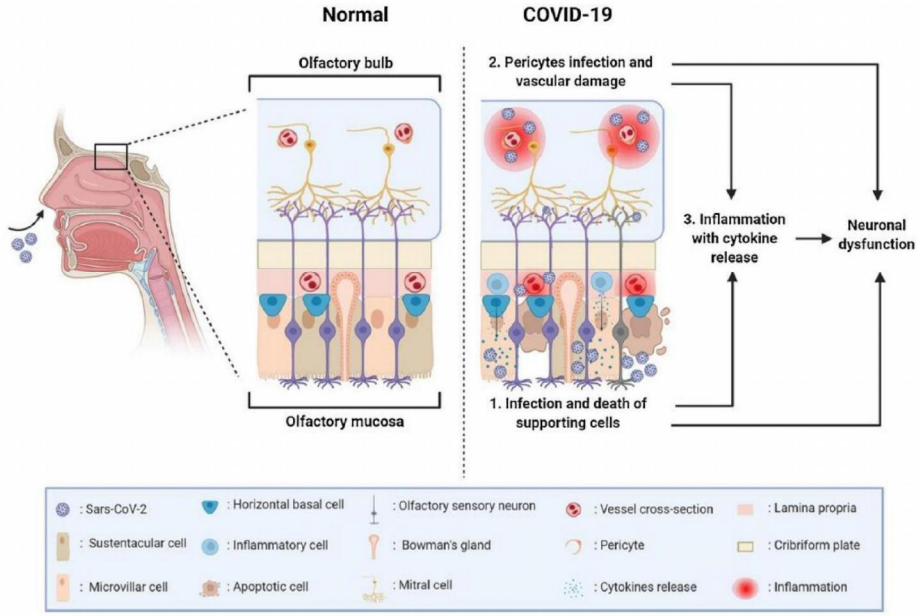
(A) **Chronic inflammation** of cardiomyocytes can result in myositis and cause cardiomyocytes death.
(B) **Dysfunction of the afferent autonomic nervous system** can cause complications such as postural orthostatic tachycardia syndrome.
(C) **Prolonged inflammation and cellular damage** prompts fibroblasts to secrete extracellular matrix molecules and collagen, resulting in fibrosis.
(D) Fibrotic changes are accompanied by increase in cardiac fibromyoblasts, damage to desmosomal proteins results in reduced cell-to-cell adhesion.

Harry Crook BMJ 2021;374:n1648

Pathophysiology hypotheses and associations:

- General
- Pulmonary
- Cardiovascular
- **Anosmia (ageusia)**
- Neurological
- Kidney

Anosmia (ageusia) purely <u>local</u> or regional pathogenesis?



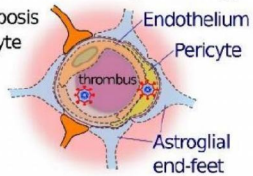
1) Infection and damage of supporting cells of the olfactory epithelium,→ inflammation
2) Infection or immune-mediated damage of endothelial cells and vascular pericytes → hypoperfusion and inflammation.
3) Inflammatory cells, cytokines and neurotoxic compounds may indirectly influence the neuronal signaling

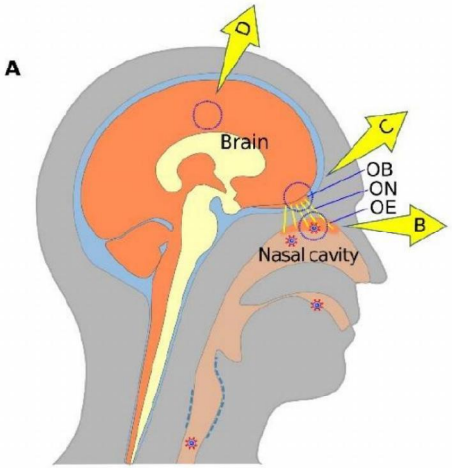
Ref 20 Andrea Mastrangelo Neuroscience Letters Jan 2021

Anosmia (ageusia) purely local or regional pathogenesis?

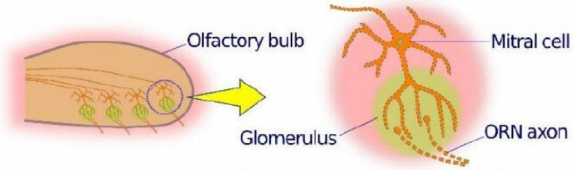
D. CNS: Hematogenous neuropathology

- Microvascular thrombosis
- Endothelium & pericyte infection/damage
- Microglia activation
- Astrogliosis



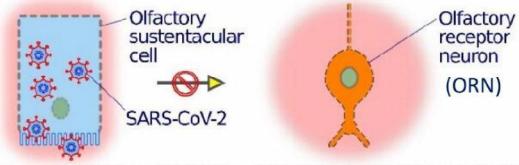


C. Possible neuropathology in the olfactory bulb (OB)



- Anterograde & trans-synaptic degeneration of ORN axons & terget neurons in the OB
- Anterograde signaling & transport of pathogenic molecules from the OE to the OB

B. Olfactory epithelium (OE): infection & pathology



Olfactory sustentacular cell (OSC):

- Infection & damage
- OE structural damage
- In persistent post-Covid anosmia
  - Chronic OE infection
  - Continuous inflammation
  - Damage to basal cells

Olfactory receptor neuron (ORN)

- Loss of support from OSCs
- Damage by inflammation, immune reactions, cytokines, PAMPs or DAMPs signaling, etc

= Pathogen- or Damage- Associated Molecular Patterns

Ref 21 Fengyi Liang Viruses Nov 2021

Pathophysiology hypotheses and associations:

- General
- Pulmonary
- Cardiovascular
- Anosmia (ageusia)
- **Neurological**
- Kidney

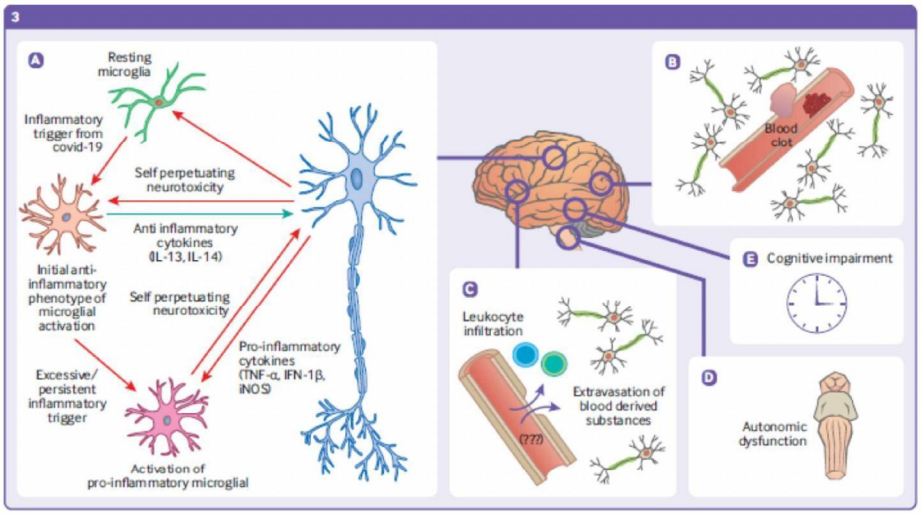
Proposed mechanisms of COVID-19 neurological sequelae

Neurological sequalae	Putative mechanism	Ref.
Ischemic stroke	Cytokine overproduction; Vascular endothelial damage, Endothelial dysfunction; Hypercoagulable state	[12–20]
Hemorrhagic stroke	Decrease in ACE-2 levels; Blood pressure increase; Coagulopathy; CVST	[21,23,24]
Encephalopathy, encephalitis	Cytokine overproduction; Vascular endothelial damage; Direct CNS invasion; Hypoxia; Autoimmunity	[9,22,25–35]
ICUAW	Cytokine overproduction; Myofiber atrophy; Direct viral damage	[42–47]
Myoclonus	Autoimmune cerebellar/brainstem damage; Hypoxia	[41]
Brain fog/Long COVID	Autoimmune; Neuroinflammation; Neurodegeneration	[9,26,35–37]
Headache	Hypoxia; Activation of peripheral trigeminal nerve endings; Cytokine overproduction; Direct CNS invasion; Hypercoagulable state	[38,39]
Guillain-Barre syndrome/Polyneur opathy	Autoimmunity/Molecular mimicry	[40]
Depression, anxiety and sleep disorders	Cytokine overproduction/Neuroinflammation; Direct CNS invasion	[48–51]
Seizure	Hypoxia; Multiorgan failure; Metabolic derangements; Cytokine overproduction; Direct CNS invasion	[1,52]

Note: CNS = central nervous system; CVSF = central venous sinus thrombosis; ICUAW = Intensive Care Unit acquired weakness

Ref 22 Samuel Ahmad J Integr. Neurosci April 2022

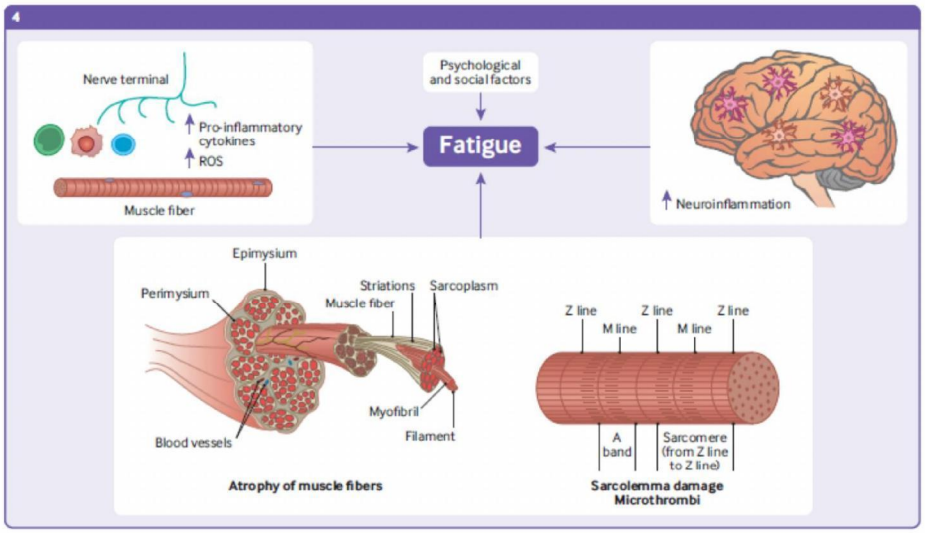
Long term sequalae of covid-19 in the central nervous system



(A) The long term immune response **activates glial cells** which chronically damage neurons.
(B) Hyperinflammatory and hypercoagulable states lead to an increased risk of thrombotic events.
(C) Blood-brain barrier damage and dysregulation results in pathological permeability, allowing blood derived substances and leukocytes to infiltrate the brain parenchyma.
(D) Chronic inflammation in the brainstem may cause autonomic dysfunction.
(E) The effects of long covid in the brain can lead to cognitive impairment.

Harry Crook BMJ 2021;374:n1648

Possible mechanisms causing post-covid-19 fatigue



A range of central, peripheral, and psychological factors may cause chronic fatigue in long covid.
Chronic inflammation in the brain, as well as at the neuromuscular junctions, may result in long term fatigue.

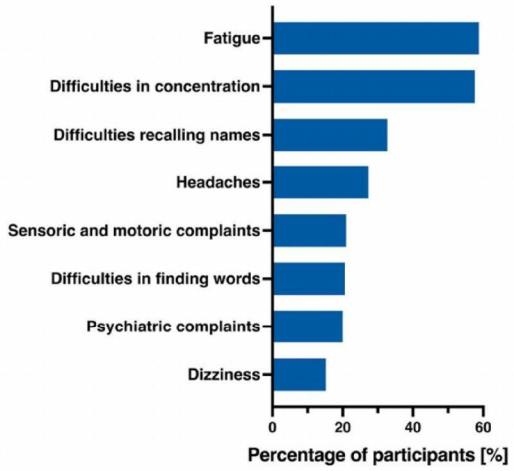
In skeletal muscle, sarcolemma damage and fiber atrophy and damage may play a role in fatigue,
as might a number of psychological and social factors

Harry Crook BMJ 2021;374:n1648

Post-COVID-19 Syndrome is Rarely Associated with Damage of the Nervous System: Prospective cohort of 171 patients with neuro-psych long-COVID complaints

Table 1 Demographics, severity of COVID-19, and medical history of patients

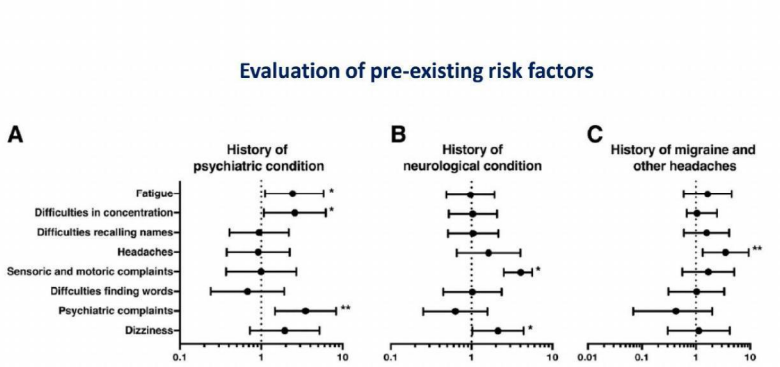
Demographics	
Participants	171
Age, years	45.2 ± 12.7 (18–74)
Female	66.7%
Severity COVID	%
Mild	34.5
Moderate	64.9
Severe	0.6



Medical history	%
Previous cardiovascular condition (arterial hypertension (86%), myocardial infarction (4%), other heart diseases (10%))	28.3
Previous neurological conditions (Migraine (44%), stroke (16.3%), MS (4.1%), PNP (8.2%), CPS (8.2%), epilepsy (4.1%), post-infectious fatigue (2%), others (12.2%))	29.0
Previous psychiatric preconditions (Depression (66.7%), anxiety disorder (20.1%), post-traumatic stress disorder (3.3%), somatic disorder (3.3), adjustment disorder (3.3%), borderline disorder (3.3%))	19.0

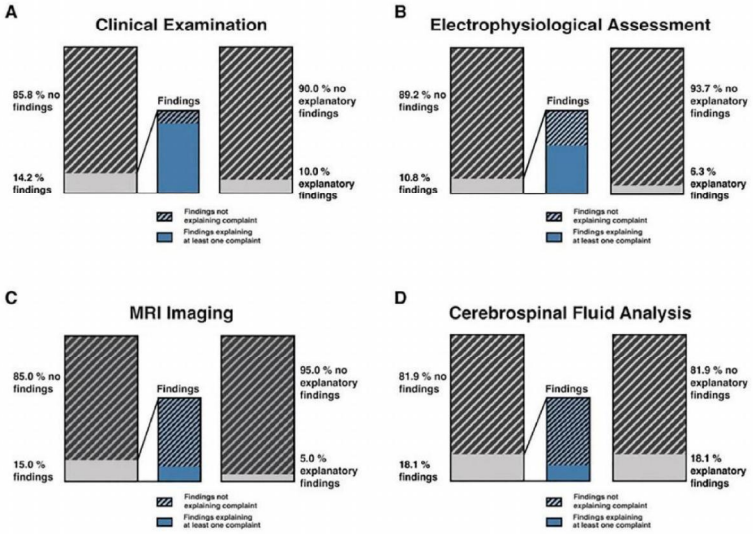
Ref 23 5.1.2a Fleischer Neurol Ther Aug 2022

Post-COVID-19 Syndrome is Rarely Associated with Damage of the Nervous System: prospective cohort of 171 patients with neuro-psych long-COVID complaints



Few risk factors identified:

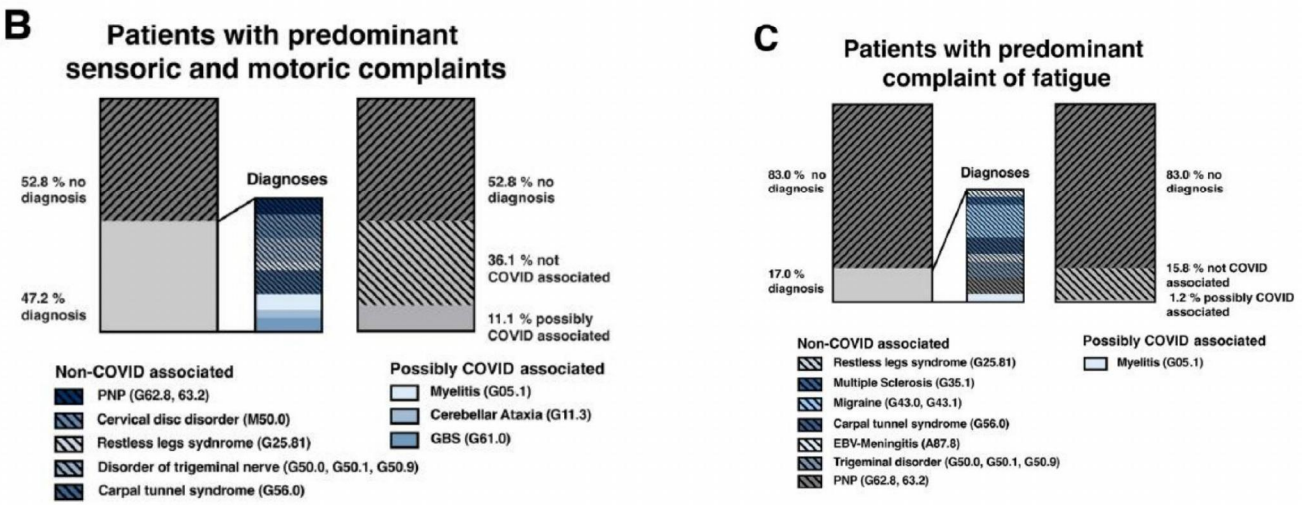
A) Psych history → fatigue, concentration and psychiatric complaints
B) Neurol history → sensory and motoric complaints
C) Migraine → headache



Thorough examinations → few diagnoses

Ref 23 5.1.2a Fleischer Neurol Ther Aug 2022

Post-COVID-19 Syndrome is Rarely Associated with Damage of the Nervous System: prospective cohort of 171 patients with neuro-psych long-COVID complaints



PNP = polyneuropathy; GBS = Guillain Barré Syndrome

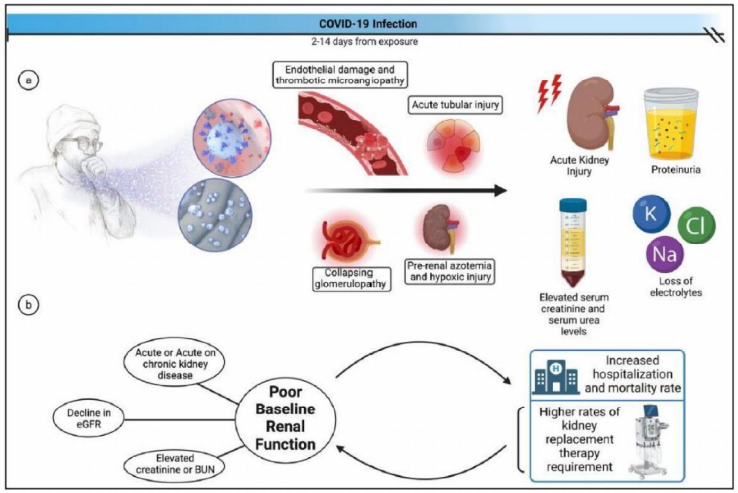
Ref 23 5.1.2e Fleischer Neurol Ther Aug 2022

Pathophysiology hypotheses and associations:

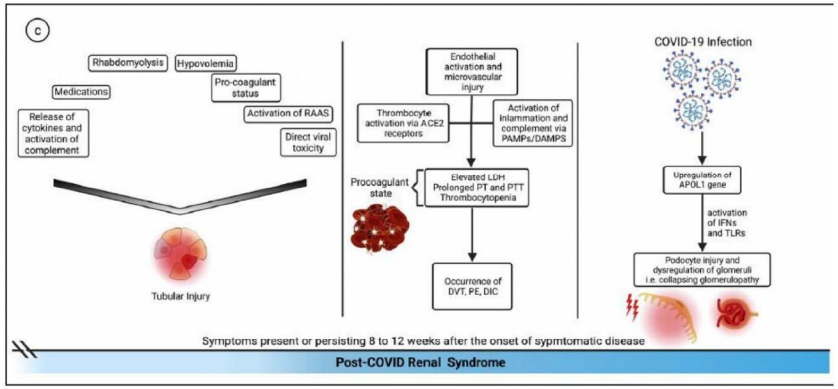
- General
- Pulmonary
- Cardiovascular
- Anosmia (ageusia)
- Neurological
- **Kidney**

Post-acute COVID-19 syndrome and kidney diseases

Acute phase



Chronic phase



1) In acute phase: chronic kidney disease and development of acute kidney injury (AKI) →high mortality and morbidity rates.
2) In the 6-to-12-month follow-up period: a decline in renal function has been observed even in patients without AKI in acute phase.
3) There are no guidelines regulating the follow-up period or therapeutic alternatives.

Ref 27 Sidar Copur J Nephrology (2022) vol 35 p795–805

The LONG COVID CONUNDRUM

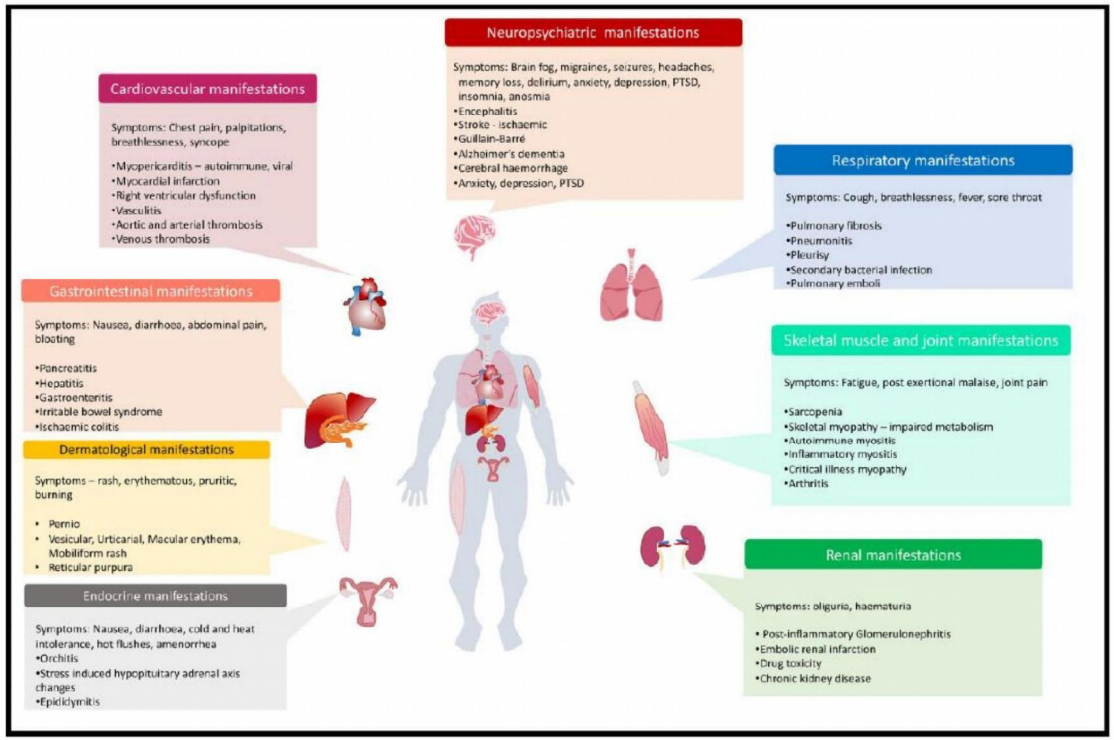
1) Definition, scope and classification

2) Risk factors

3) Pathophysiology: hypotheses and associations

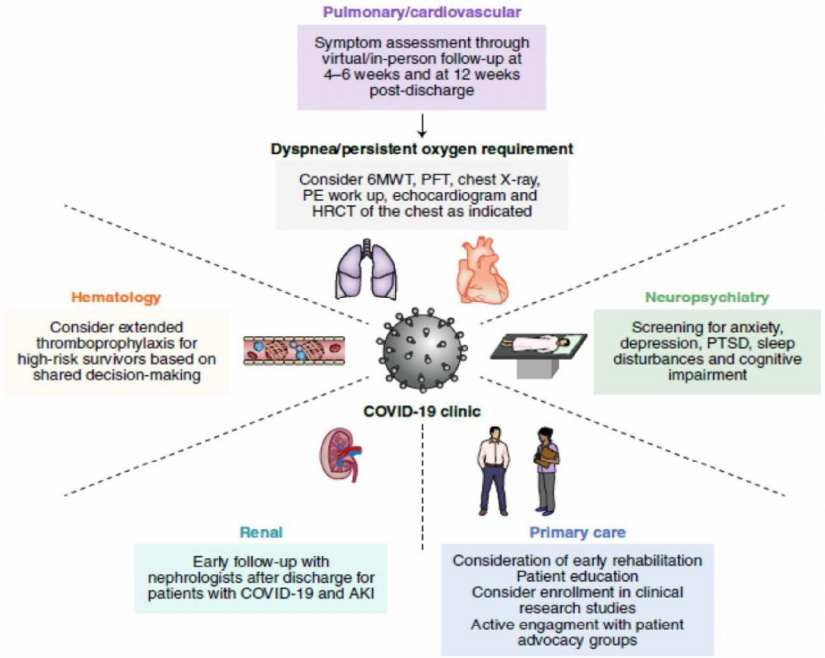
4) Management

Long COVID has many faces



Raman Eur Heart J Oct 2022 vol 43 p. 1157

Interdisciplinary management in COVID-19 clinics



Prioritization for those at high risk for PACS: with **severe acute COVID-19** and/or requirement **ICU**, **advanced age** and **comorbidities**: pre-existing respiratory disease, obesity, diabetes, hypertension, chronic cardiovascular disease, chronic kidney disease, post-organ transplant or active cancer.

Ref 1 Ani Nalbandian Nat Med April 2021

Therapeutic management of Long COVID

1) General or respiratory rehabilitation = indicated if long COVID-19 persists in patients with severe COVID-19 treated in ICU or patients >65 years of age

2) Medicines for persistent respiratory symptoms? No clear cut advantage of corticoids, antihistaminic etc

3) Thromboprophylaxis: not routinely. Decision based on assessment of thrombotic and bleeding risk.

4) **Smell and taste disturbance**: no specific treatment, but olfactory training may help.

5) Fatigue: no specific treatment

6) Mental and psychological problems: no specific treatment

7) Cognitive disturbance and headache: no specific treatment

Table 5. Drugs used for the treatment of headache

Category	Drug	Mechanism	Daily dose range	Side effects
Prophylactic treatment	Propranolol	Beta-blocker	20 - 160 mg	Fatigue, dizziness, depression, vivid dreams
	Flunarizine	Calcium channel blocker	5 - 10 mg	Weight gain, sleepiness, dry mouth, dizziness, hypotension, depression, Parkinsonism
	Amitriptyline	Tricyclic antidepressant	2.5 - 50 mg	Weight gain, constipation, asthenia, dizziness, drowsiness, fatigue, blurred vision, dry mouth
	Topiramate	Epilepsy medication	12.5 - 150 mg	Paresthesia, weight loss, memory impairment
Acute-phase treatment	Frovatriptan	Triptan	2.5 - 5 mg	Triptan sensation (numbness, throbbing, strange feeling, warmth, burning, cold, tightness in body including neck and chest), dizziness, drowsiness, fatigue, asthenia, headache, nausea
	Naratriptan	Triptan	1 - 2 mg	Triptan sensation, dizziness, drowsiness, fatigue, asthenia, headache, nausea
	Zolmitriptan	Triptan	2.5 - 7.5 mg	Triptan sensation, dizziness, drowsiness, fatigue, asthenia, headache, nausea

Ref 6 Yoonjung Kim Infect Chemother. 2022 Sep;54(3):566-597

Ongoing Clinical trials for long COVID

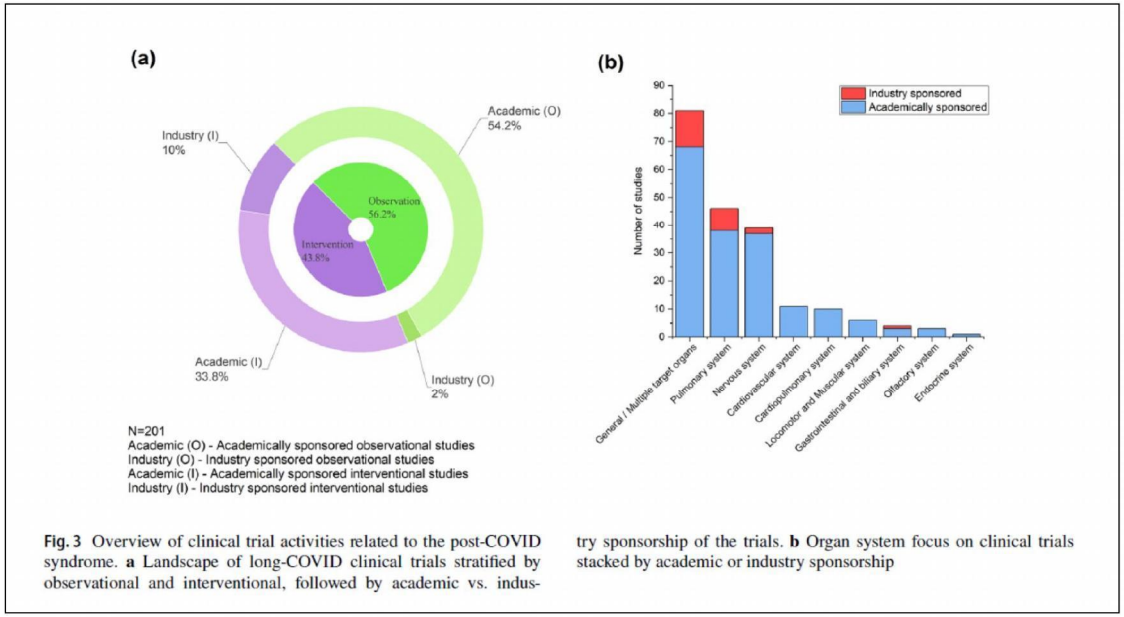
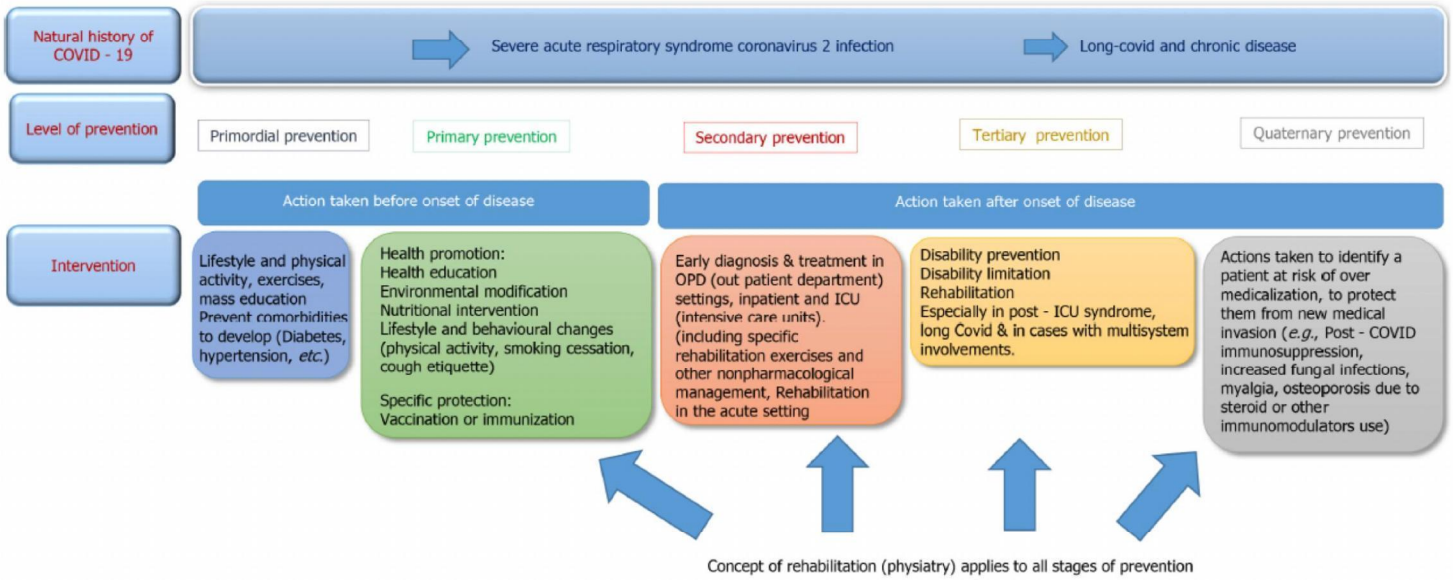


Fig. 3 Overview of clinical trial activities related to the post-COVID syndrome. **a** Landscape of long-COVID clinical trials stratified by observational and interventional, followed by academic vs. industry sponsorship of the trials. **b** Organ system focus on clinical trials stacked by academic or industry sponsorship

Ref 2 Anushri Umesh Infection 30 April 2022

Prevention and Rehabilitation perspective of long COVID



Ref 24 Raktim Swarnakar World J. Method. July 2022

Long COVID clinics

UK https://www.england.nhs.uk/coronavirus/post-covid-syndrome-long-covid/ 90 clinics

US https://www.beckershospitalreview.com/patient-safety-outcomes/13-hospitals-health-systems-that-have-launched-post-covid-19-clinics.html 66 sites

US NIH information: https://covid19.nih.gov/covid-19-topics/long-covid#long-covid-resources-1

Germany https://www.klinikkompass.com/kliniken-fuer-post-covid-patienten/ 36 also dozen

France https://www.iledefrance.ars.sante.fr/covid-long-qui-contacter-quelle-organisation-des-soins-en-ile-de-france

Long COVID Nederland https://www.linkedin.com/company/petitie-long-covid-nederland-pasc/

Belgium? **No information on the internet.**

The Long-COVID conundrum

A very popular theme: over 7900 papers in PubMed

A large variety of symptoms has been associated, but most studies are not properly controlled: frequency is very variable.

- Some symptoms can be objectivated (pulmonary, cardiovascular, kidney)
- Others are more difficult to pinpoint (e.g. neurological, fatigue ...)

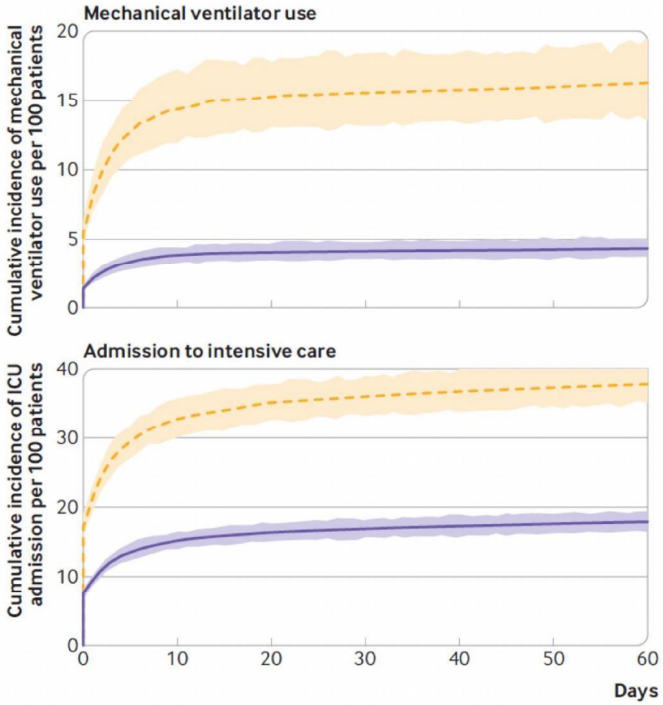
There is a rather clear set of risk factors: co-morbidities, immune suppression, age, previous COVID-19. Less frequent with omicronVaccination has a partial protective effect.

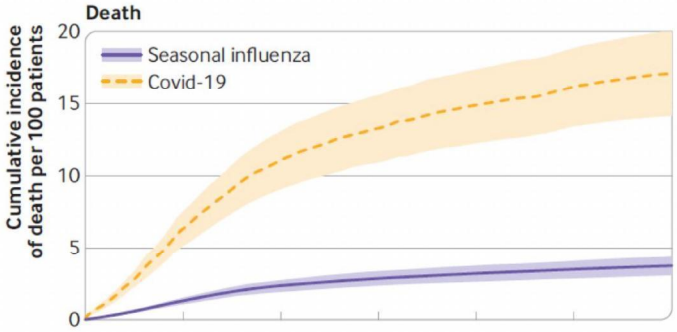
Proposed pathophysiological mechanisms include viral persistence, hyper-inflammation and hyper-coagulation, but remain largely hypothetical.

No validated treatment guidelines. Lack of validated phase 3 trials.
Management needs to be multi-disciplinary and remains difficult.

Additional slides

Comparison of adverse outcome in COVID-19 (Feb -June2020) vs seasonal influenza (2017-2019)

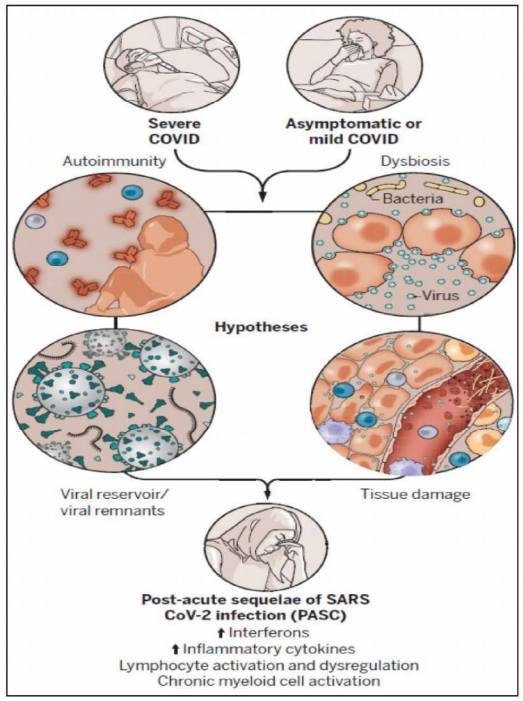




Outcome	Covid-19 *v* seasonal influenza Adjusted hazard ratio (95% CI)	Excess outcomes per 100 patients (95% CI)
Death		16.85 (14.85 to 18.99)
Mechanical ventilator use		11.29 (9.62 to 13.14)
Intensive care unit admission		19.80 (17.81 to 21.87)

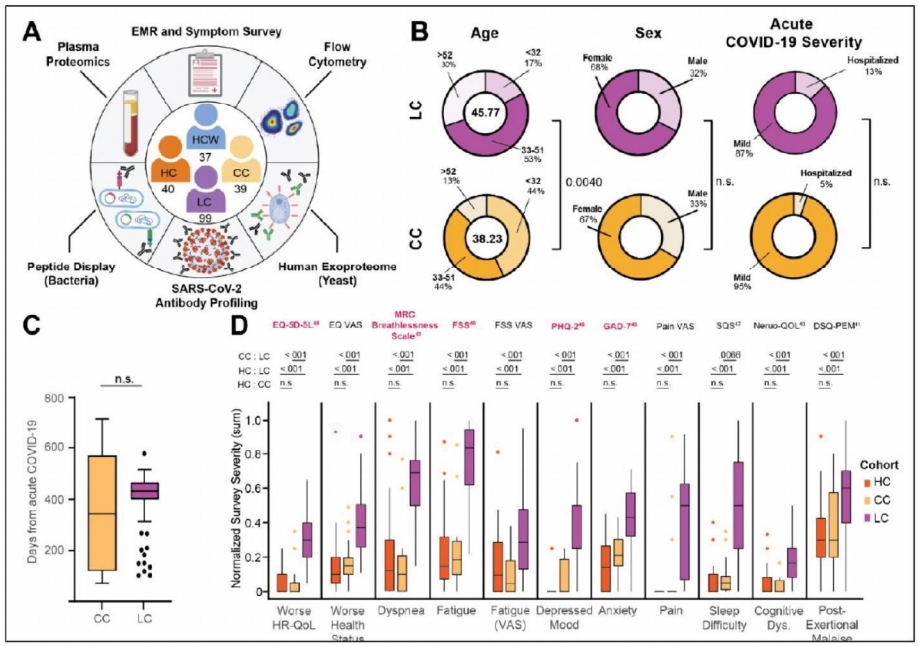
Yan Xie BMJ 2020;371:m4677

The immunology and immunopathology of COVID-19



A fraction of patients with either severe or mild COVID-19 develop a variety of new, recurring, or ongoing symptoms 4 or more weeks after infection.
Analyses in people with PASC reveal key inflammatory cytokines and cellular activation phenotypes that are elevated over nonPASC convalescents.

Distinguishing features of Long COVID identified through immune profiling



Long-COVID slightly older;
more hospitalized (ns),
but equal sex ratio

Over 1 year after acute episode

Many symptoms

HC = healthy controls; CC = convalescent controls (fully recovered) ; LC = long COVID

Jon Klein medRxiv 10 August 2022

Risk Factors and Putative Pathophysiology of Long-COVID

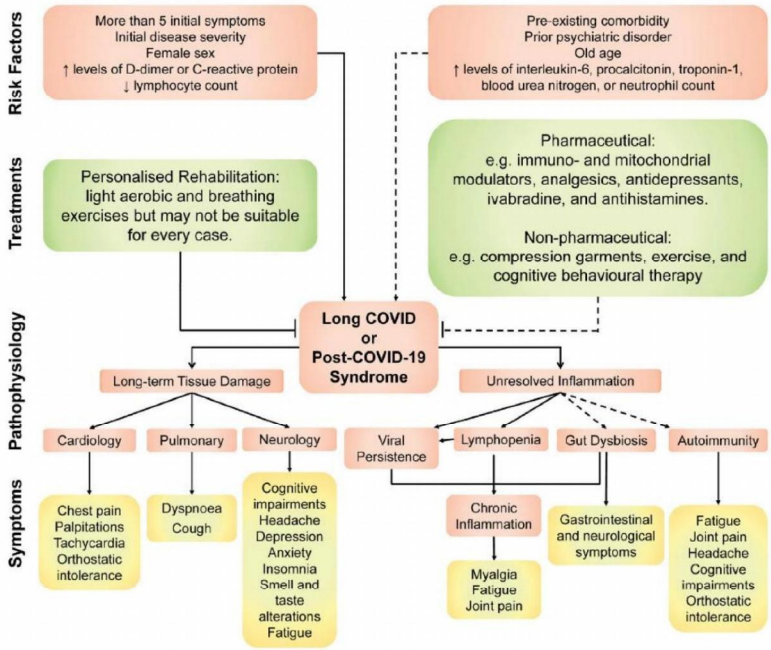


Figure 1. An overview of the symptoms, putative pathophysiology, associated risk factors, and potential treatments involved in long COVID. Note: Dashed lines represent areas where evidence is relatively lacking compared to non-dashed lines. (Color online only).

Shin Jie Yong Infectious Diseases (2021) vol 53 p. 737

Proposed subtypes of post-COVID-19 syndrome

1) Non-severe COVID-19 multi-organ sequelae (NSC-MOS) = Multi-organ symptoms lasting for ≥3 months after acute COVID-19 especially fatigue, dyspnoea and cognitive impairments. **R/**Personalised, multidisciplinary rehabilitation

2) Pulmonary fibrosis sequelae (PFS): impaired lung function or respiratory symptoms for ≥3 months after acute COVID-19, especially severe COVID. **R/** pulmonary rehabilitation, (hyperbaric) oxygen, anti-fibrotic drugs (?), Ca++ channel blocker (?)

3) Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Disabling fatigue, unrefreshing sleep, post-exercitional malaise and either cognitive impairment or orthostatic intolerance lasting for ≥6 months after acute COVID-19.
R/ Personalized rehabilitation, probably sleep inducers; anti-depressants;

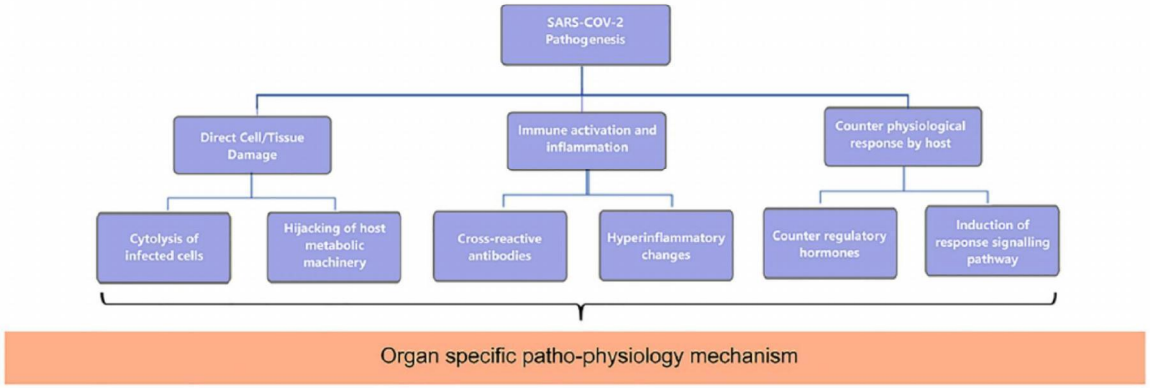
4) Postural orthostatic tachycardia syndrome (POTS): Dysfunction of the autonomic nervous system with orthostatic hypotension, dizziness, palpitations, blurred vision, headache, generaliZed weakness, exercise intolerance, and fatigue.
R/ Increased fluid and salt intake; Compression garments/stockings; Non-upright exercises
Propranolol (beta-blocker); Midodrine (vasopressor); Ivabradine (If ion channel blocker)

5) Post-intensive care syndrome (PICS): Severe-to-critical illnesses in need of ICU level of care, from which full recovery is difficult Physical weakness, cognitive and mental problems lasting for many nmonths
R/ Physical rehabilitation and mental support. Besides possibly: anti-coagulants; RAAS inhibitors, beta-blokkers, Statins,….

6) **Medical or clinical sequelae (MCS)** = deterioration of the health of survivors or unmasking of chronic diseases, leading to medical or clinical sequelae (MCS) in need of medical attention, such as diabetes, respiratory, cardiovascular, gastrointestinal and neurological diseases and mental and behavioural disorders.
R/ Standard therapy of these disorders

Shin Jie Yong Rev Med Virol Aug 2021

Proposed pathophysiological mechanisms for long-COVID



Organ specific patho-physiology mechanism

Nervous system	Pulmonary system	Cardiovascular system	Endocrine System and Metabolic function	Gastrointestinal and Biliary system	Reproductive system	Other patho-physiological changes
1. Direct neurotrophism and inflammation	1. Fibrotic pulmonary parenchymal remodelling	1. Acute myocarditis and Cardiomyopathy	1. Autoimmune attack against pancreatic beta-cell antigens	1. Down regulated cytokines such as IFN-γ, CXCL8, CXCL2 and IL-1β	1. Impaired Blood-testis barrier (BTB)	1. Myopathy (e.g. loss of myosin, reduced myosin:actin ratio)
2. Vestibule-cochlear neuritis	2. Local effects of inflammatory response (e.g. CRP↑, IL-6↑, TNF-α↑)	2. Auto-antibodies against GPCRs	2. Hyperglycaemia induced due to hypometabolic state and steroid medication	2. Intrahepatic microangiopathy	2. Dysfunctional hypothalamus-pituitary-gonad axis (e.g. dysregulated gonadotropins and di-hydro-testosterone balance)	2. Biochemical markers in blood plasma (e.g. Taurine↑, GlycA↑, kynurenine/tryptophan↑, glutamine/glutamate ratio↓)
3. Myalgic encephalomyelitis	3. Infiltration of cells in lungs e.g. Megakaryocytes, Neutrophils	3. Dysregulation of Renin-Angiotensin-Aldosterone (RAA) system	3. Dysfunction of hypothalamic-pituitary axis (e.g. Dysregulated TSH-T3 axis and ACTH-Cortisol axis)	3. Cholangiopathy	3. Viral orchitis and testicular injury (inflammation of testicles)	3. Oxidative stress driven by COVID-19
4. Limbic encephalitis	4. Increase in biomarkers such as Lipocalin-2, MMP-7 and HGF	4. CV effects of elevated inflammatory cytokines (e.g. CRP, IL-6, TNF-α, IFN-γ, IL-1β)	4. Thyroiditis/ thyrotoxicosis		4. Elevated Testosterone, di-hydro testosterone levels (elevated)	4. Mitochondrial ROS and activation HIF-1α
5. Longitudinally extensive transverse myelitis (LETM)	5. Vagus nerve inflammation and dysfunction	5. Increased infiltration of cells e.g. Megakaryocytes, Neutrophils			5. Hypogonadism	5. Disrupted of one-carbon metabolism or methyl-group transfer
6. Acute disseminated encephalomyelitis (ADEM)		6. Formation of Neutrophil extracellular traps (NETs)			6. Reduced sperm motility	6. Activation of oncogenic pathways (e.g. JAK-STAT and NF-κB pathways)
7. Neuro-inflammation in hypothalamic microglia		7. Platelet activation and Immuno-thrombotic mechanisms			7. Inflammation of seminiferous tubules	7. Elevated pro-inflammatory cytokines (e.g. IL-1, IL-6, IL-8, and TNF-α), T-cell depletion)
8. Hypometabolic state/ altered metabolic states of neurons		8. Coagulopathy (through activation VWF, Factor XII)			8. Infiltration of inflammatory cells	8. Inflammasome: Caspase-1 mediated cell death (Pyroptosis) in T-cells
9. Disruption of mitochondrial function in neurons and microglia		9. Activations of Contact-dependent pathway of coagulation				
10. Immune-mediated disruption of the autonomic nervous system		10. Hypoxia-inducible transcription factors and coagulopathy				

Abbreviations: C-Reactive Protein (CRP); Interferon gamma (IFN-γ); Tumor necrosis factor-α (TNF-α); Interleukin-1β (IL-1β); Interleukin-1 (IL-1); Interleukin-6 (IL-6); Interleukin-8 (IL-8); Matrix metalloproteinase-7 (MMP-7); Hepatocyte growth factor (HGF); GPCR—G-protein coupled receptors; von Willebrand factor (vWF);); Thyroid stimulating hormone (TSH); Triiodothyronine (T3); Adrenocorticotropic hormone (ACTH); Hypoxiainducible factor 1α (HIF-1α); Reactive oxygen species (ROS); Chemokine (C-X-C motif) Ligand (CXLC-2, CXCL-8 etc.)

Standardized Quality of Life assessment

TABLE 1 Study characteristics and persistent symptoms and quality of life instrument used in individual studies

Author, country	Sample size (N)	Follow-up after discharge (days), mean (±SD/range)	Mean age	Male (N)	ICU	Persistent symptoms	Quality of life (QoL) instruments
Chopra et al., USA[24]	1250	60	62	648	165	Cough, dyspnea, anosmia, chest pain, mental health	EQ-VAS
Carfì et al., Italy[25]	143	36.1 (12.9)	56	90	18	Fatigue, cough, dyspnea, anosmia, headache, arthralgia, chest pain	EQ-VAS
Haplin et al., UK[14]	100	48 (10.3)	58.5	54	32	Fatigue, dyspnea, mental health	EQ-VAS EQ-5D-5L
Taboada et al., Spain[10]	91	180	65	59	91	Fatigue, cough, anosmia, arthralgia, chest pain, sleeping disturbances	EQ-VAS EQ-5D-5L
Jacobs et al., USA[6]	183	35	57	112		Fatigue, cough, dyspnea, anosmia, headache, arthralgia	EQ-VAS
Tabacof et al., USA[26]	84	151	44	26		Fatigue, headache	EQ-VAS
Valent et al., France [27]	54	90	62	39	54	NA	EQ-VAS EQ-5D-5L
Arab-Zozani et al., Iran[11]	409	30	58.4	247	74	NA	EQ-5D-5L
Mandal et al., UK[28]	384	54 (47–59)	59.9	238		Fatigue, cough, dyspnea, anosmia, headache, arthralgia, sleeping disturbances, mental health	EQ-VAS
Huang et al., China[29]	1733	153 (146–160)	57	897	76	Fatigue, cough, dyspnea, anosmia, headache, arthralgia, chest pain, sleeping disturbances	EQ-VAS EQ-5D-5L
Garrigues et al., France[15]	120	110.9 (±11.1)	63.2	75	24	Fatigue, cough, dyspnea, anosmia, chest pain, sleeping disturbances	EQ-VAS
Moreno-Pérez et al., Spain[30]	277	77 (72–85)	62	146	24	Fatigue, cough, dyspnea, anosmia, headache, arthralgia	EQ-VAS
Total	4828						

Twelve studies between March 2020 and Mach 2021 on almost 5000 subjects

1) **EQ-VAS** is a patient's subjective assessment of generic health ranging from 0 to 100 (or 0 to 1)
2) **EQ-5D-5L** is a validated questionnaire to evaluate a patient's quality of life by five factors: mobility, selfcare, usual activities, pain or discomfort, and anxiety or depression. Categorization divided into five levels that range from no problems to extreme problems

Preeti Malik J Med Virol August 2021

Standardized Quality of Life assessment

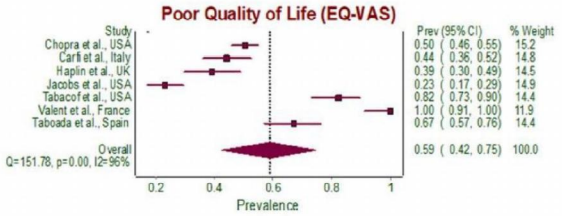
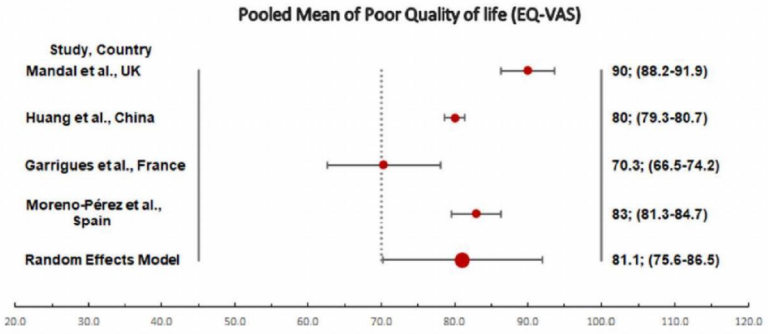


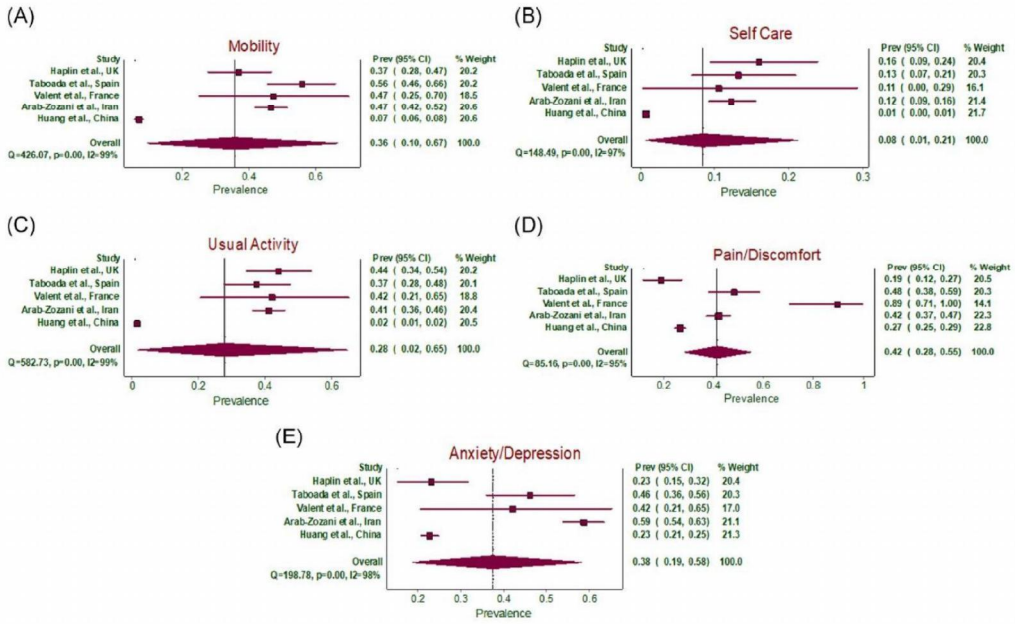
FIGURE 2 Forest plot of pooled prevalence of poor quality of life (EQ-VAS) in post-COVID-19 patients. CI, confidence interval



Twelve studies between March 2020 and Mach 2021 on almost 5000 subjects

1) **EQ-VAS** is a patient's subjective assessment of generic health ranging from 0 to 100,

Standardized Quality of Life assessment



Twelve studies between March 2020 and Mach 2021 on almost 5000 subjects

1) **EQ-5D-5L** is a validated questionnaire to evaluate a patient's quality of life by five factors: mobility, selfcare, usual activities, pain or discomfort, and anxiety or depression. Categorization divided into five levels that range from no problems to extreme problems

Preeti Malik J Med Virol August 2021

Neuropsychiatric assessment

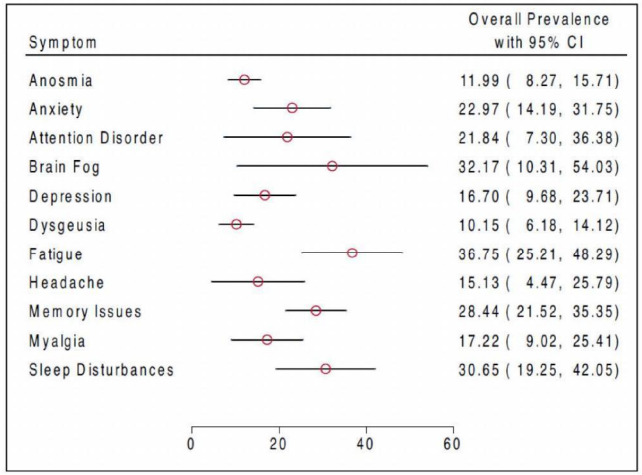
18 studies, encompassing a total of 10,530 patients, were analysed:

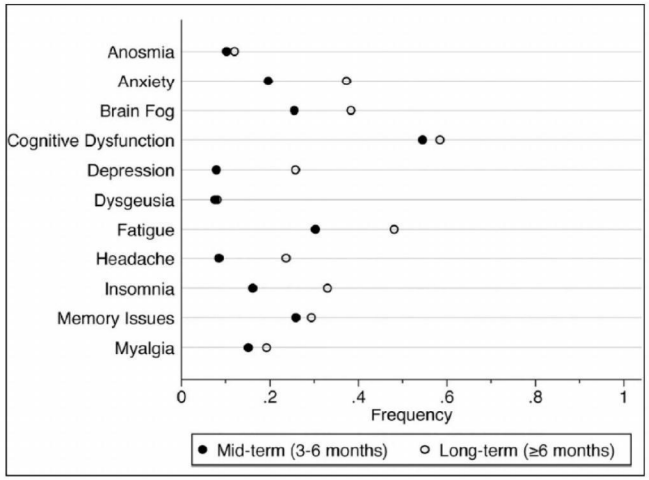
Table 1
Descriptive statistics for overall study population, n (%), stratified by hospitalisation.

	All Patients (N=10,530)	Non-hospitalised (N= 4,747)	Hospitalised (N=5,783)
Demographic Characteristics			
Male[a]	4115/10140 (41)	924/4245 (22)	2975/5464 (54)
Age[b], mean, (SD)	52 (10)	46 (4)	57 (7)
Acute COVID-19 Information			
Hospital admission	6107/10530 (58)	324/4747 (7)	5783/5783 (100)
Duration of hospital admission[c], days (SD)	12 (4)	-	12 (4)
ICU admission	522/4045 (13)	-	522/4045 (13)
Duration of ICU admission[d], days (SD)	13 (4)	-	13 (4)
Neurological symptoms of post-COVID-19 syndrome			
Anosmia	357/3164 (11)	93/505 (18)	264/2659 (10)
Attention Disorder	271/1207 (22)	73/130 (56)	198/1077 (18)
Brain Fog[e]	1557/4329 (36)	1515/3914 (39)	42/415 (10)
Confusion[e]	95/949 (10)	74/152 (49)	21/797 (3)
Dysgeusia	246/2703 (9)	86/505 (17)	160/2198 (7)
Fatigue	3197/7173 (45)	2430/4747 (51)	767/2426 (32)
Headache	1502/7437 (20)	1398/4267 (33)	104/3170 (3)
Memory Issues[e]	1584/5033 (29)	1311/3892 (34)	273/1141 (24)
Movement Disorder	28/857 (3)	-	28/857 (3)
Myalgia	1373/7555 (18)	1159/4267 (27)	214/3288 (7)
Pain	582/2086 (28)	107/350 (31)	475/1736 (27)
Paraesthesia	78/1218 (6)	-	78/1218 (6)
Neuropsychiatric symptoms of post-COVID-19 syndrome			
Anxiety	598/3104 (20)	198/632 (31)	400/2472 (16)
Depression	480/3104 (15)	173/632 (27)	307/2472 (12)
PTSD	135/964 (14)	35/130	100/834 (12)
Sleep disturbance	2411/7993 (30)	1411/3892 (36)	1000/4101 (24)

Very remarkably: most neurological and neuropsychiatric symptoms after 3 months were **more common in non-hospitalized patients** !

Neuropsychiatric assessment





Very remarkably: most neurological and neuropsychiatric symptoms rather **increase on the longer term** (> 6 months) !

Clinical evaluation and management of Long COVID

WHO definition: symptoms and/or signs occurring during or after the acute COVID-19 phase
- that are not explained by other diagnosesµ
- that persist for > 2 months

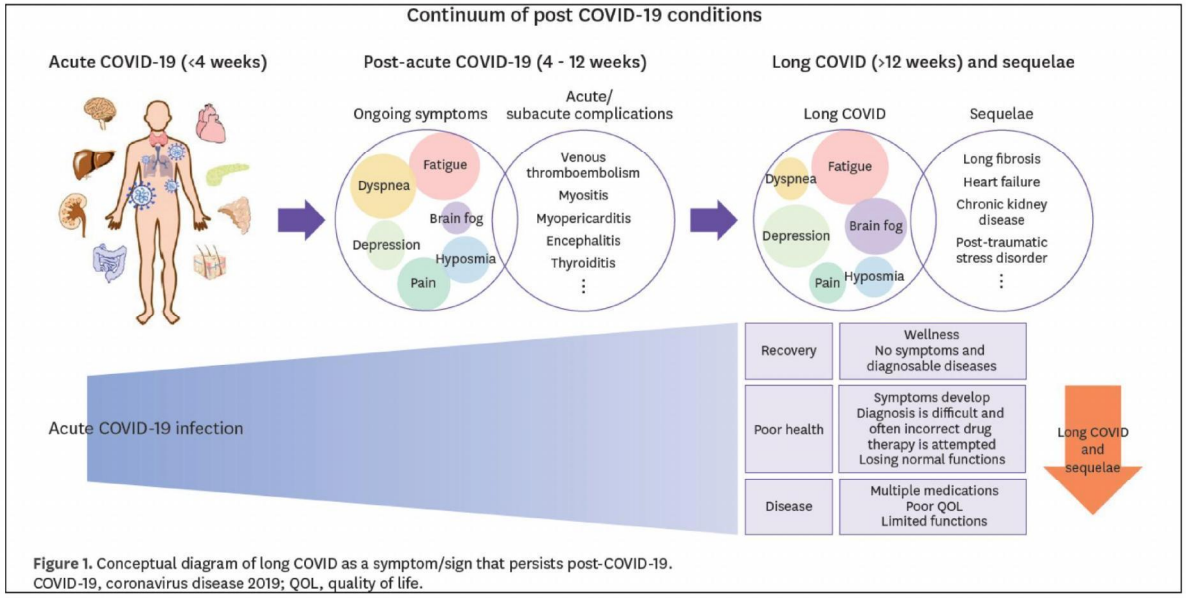
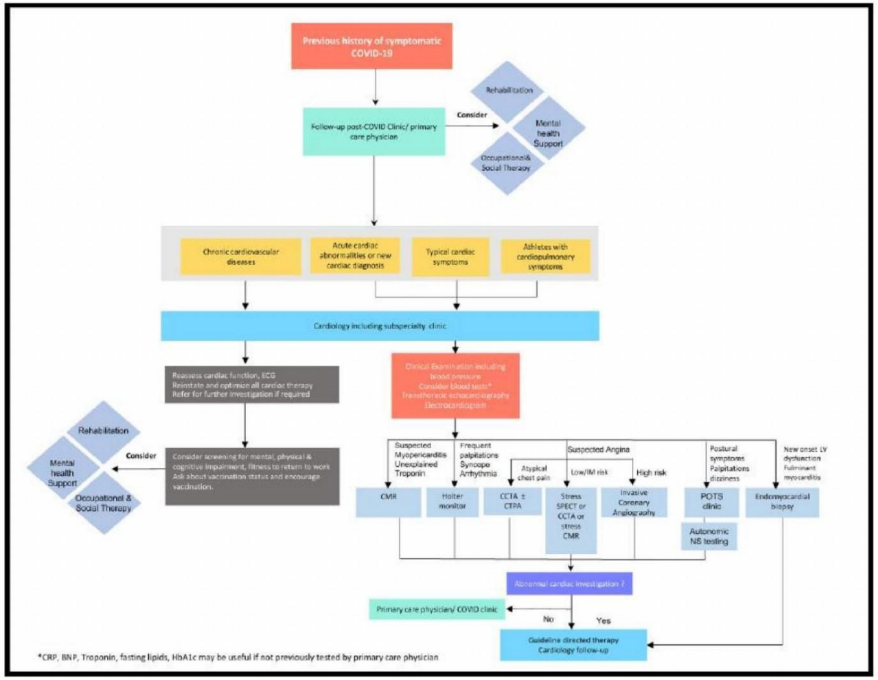


Figure 1. Conceptual diagram of long COVID as a symptom/sign that persists post-COVID-19.
COVID-19, coronavirus disease 2019; QOL, quality of life.

Yoonjung Kim Infect Chemother. 2022 Sep;54(3):566-597

Long COVID with a cardiovascular focus

Suggested algorithm for management of post-acute cardiovascular sequelae



BNP, B-type natriuretic peptide;
CCTA, coronary computed tomography angiography;
CMR, cardiac magnetic resonance;
CRP, C-reactive protein;
CTPA, computed tomography pulmonary angiography;
ECG, electrocardiogram;
HbA1c, glycated haemoglobin;
NS, nervous system;
POTS, postural orthostatic tachycardia syndrome;
Trop, troponin.

Ref 19 Raman Eur Heart J Oct 2022 vol 43 p. 1157