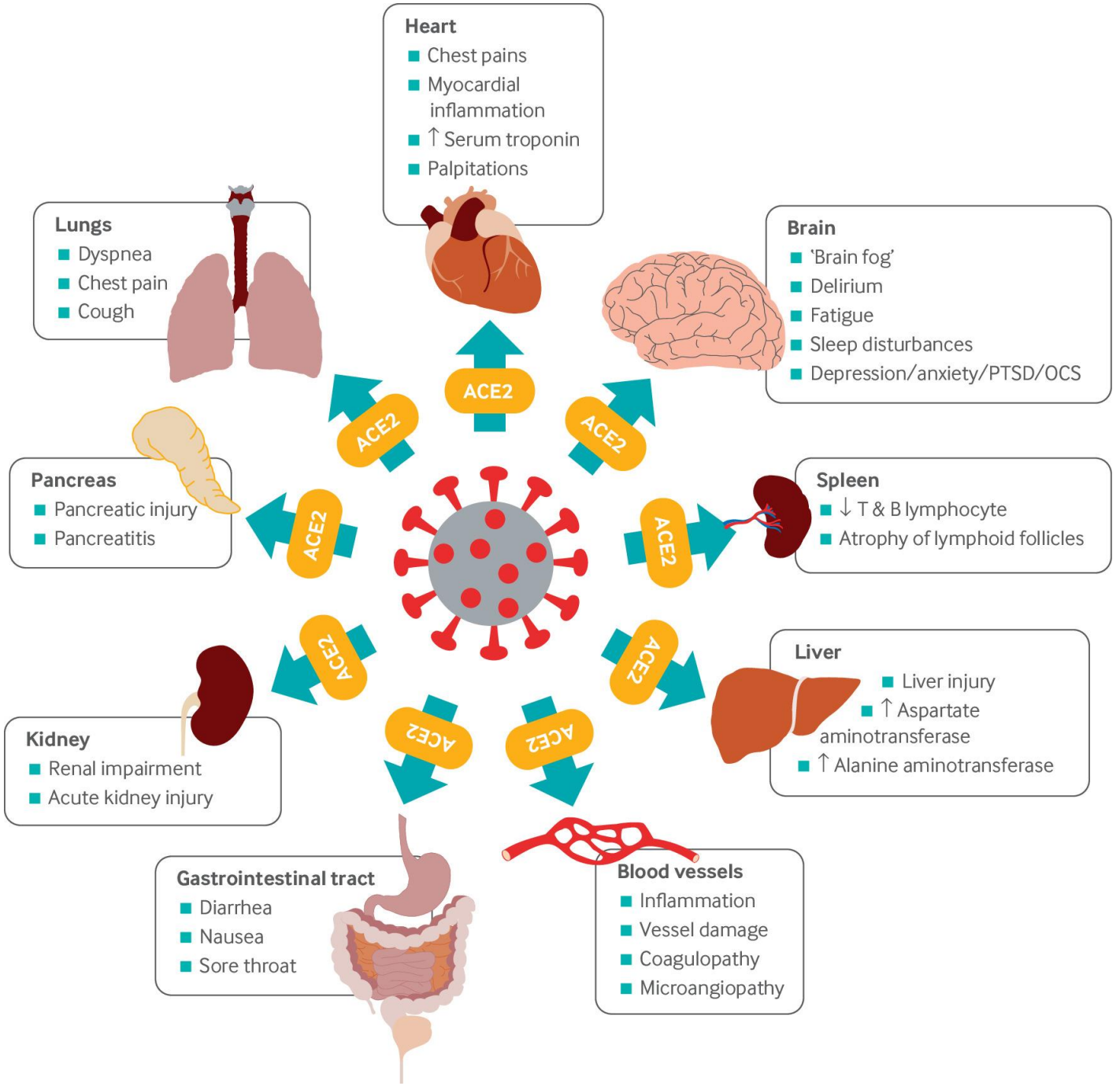
What organs and systems can be affected?

- Immune system
- Brain and central nervous system
- Endocrine
- Cardiovascular
- Pulmonary
- Gastrointestinal
- Kidneys
- Liver
- Spleen
- Pancreas
- Musculoskeletal
- Skin

Organs potentially affected by COVID-19, all of which express the ACE2 receptor

(Crook H, et al. Long covid-mechanisms, risk factors, and management. BMJ. 2021 26;374:n1648)



Prevalence of organ involvement? Scanning studies

- The UK COVERSCAN study scanned patients at 4 months and found evidence of organ impairment in 66%, comprising: lungs (33%), heart (32%), pancreas (17%), kidneys (12%), liver (10%) and spleen (6%). 23% had mild systolic dysfunction and 11% had evidence of myocarditis, which was associated with more severe disease. (Dennis A, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open. 2021 Mar 30;11(3):e048391)
- . There were several issues with this study:
  - there was no control group
  - the study was funded by the National Consortium of Intelligent Medical Imaging (NCIMI), and one of the authors of the paper is the CEO of a company supplying MRI scanners.
- Another UK scanning study at 2-3 months found abnormalities in lungs (60%), heart (26%) liver (10%) and kidneys (29%) but there were also changes in the thalamus, posterior thalamic radiations and sagittal stratum on brain MRI, indicating impaired cognitive performance, specifically in the executive and visuospatial domains. (Raman B, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021 Jan 7;31:100683)
- A scanning study at 4 months in those with suspicion of organ involvement, found that 44% had pathological findings; the remainder had functional complaints without organ damage. (Kersten J, et al. Long COVID: Distinction between Organ Damage and Deconditioning. J Clin Med. 2021 Aug 24;10(17):3782)

Further observations concerning organ involvement

- An international survey found that the **mean number of body systems affected per patient was 9** (Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019).
- **There was no correlation between the patients' symptoms and the scan findings**, although organ damage was more prevalent in those who had been admitted to hospital. (Dennis A, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open. 2021 Mar 30;11(3):e048391;https://www.gov.uk/government/publications/ons-short-report-on-long-covid-22-july-2021)

Pulmonary symptoms in Long COVID

- Breathlessness, breathing difficulties, inability to take a deep breath
- Impaired exercise capacity due to reduced oxygen flow from the lungs into the bloodstream
- Fatigue
- Cough

Prevalence of pulmonary symptoms

- A Chinese study found that **76% of hospitalised COVID-19 patients were still experiencing breathing problems six months** after first getting sick. In those who had suffered severe COVID-19, the median 6-min walking distance was lower than normal reference values in approximately 25% of patients at 6 months, due to reduced oxygen flow from the lungs into the bloodstream. (Huang L, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021 Aug 28;398(10302):747-758)
- Several studies showed patients still suffering breathlessness, fatigue, reduced exercised capacity, fibrotic lung tissue and impaired diffusion capacity 3 months after hospital discharge. (Naeije R, Caravita S. Phenotyping long COVID. Eur Respir J. 2021 Aug 26;58(2):2101763)
- Persistent breathless at 5-6 weeks due to microvascular pulmonary injury after COVID-19 recovery (Dhawan RT, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19. Lancet Respir Med. 2021 Jan;9(1):107-116).
- New or worsened breathlessness was a significant symptom in hospitalised patients after 10-14 weeks (Moreno-Pérez O, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. J Infect. 2021 Mar;82(3):378-383).

Types of lung damage seen in Long COVID

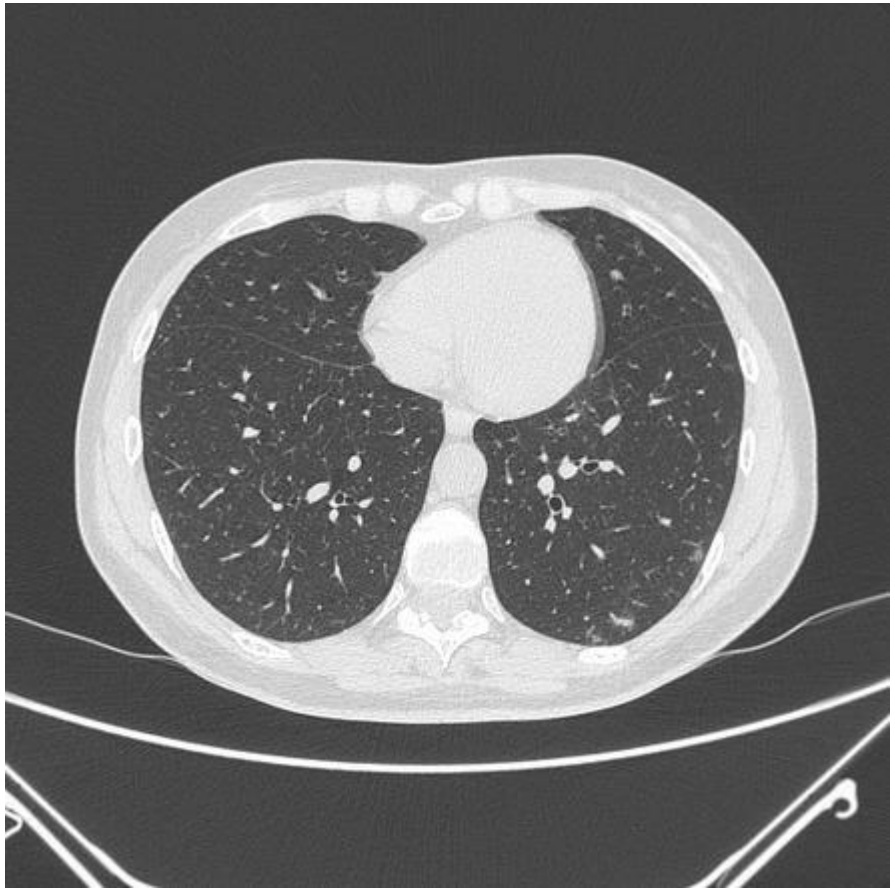
- Pulmonary fibrosis (lung scarring): reduces lung capacity, leaving patients breathless through decreased diffusion capacity
- ‘Ground glass opacities’ on CT scanning
- Other abnormalities detected by scanning
- Hypoxia, with need for supplemental oxygen

Pulmonary fibrosis

- Pulmonary fibrosis is a progressive disease, causing significant decline in pulmonary function and potential permanent pulmonary distortion, irreversible lung dysfunction or mortality within 3–5 years of the initial diagnosis. Currently considered a rare disease, COVID-19-related pulmonary fibrosis could become a common disease. (Cinar R, et al. Dual inhibition of CB1 receptors and iNOS, as a potential novel approach to the pharmacological management of acute and long COVID-19. Br J Pharmacol. 2021 Mar 26:10.1111/bph.15461; Ojo AS, et al. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med. 2020;2020:6175964).
- Fibrotic changes have been detected as early as 3 weeks after symptoms onset, regardless of the severity of the acute illness. They are more common among patients who had severe acute COVID-19 and high levels of inflammatory markers. Abnormal lung function (restrictive abnormalities, reduced diffusion capacity, small airway obstruction) have been identified 12 weeks after discharge. (Korompoki E, et al. Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021;83(1):1-16)
- Three months after hospital discharge, evidence of fibrosis can be detected on chest computed tomography of 25%-65% of patients, (Zhao YM, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020 Aug;25:100463; Shah AS, et al. A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. Thorax. 2021 Apr;76(4):402-404).
- 35% of patients who recovered from severe disease developed fibrotic-like changes in the lung within 6 months. Some of these patients complained of sustained respiratory symptoms and 26% revealed pulmonary diffusion abnormality. (Han X, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology. 2021;299(1):E177-E186)
- A meta-analysis found that approximately 30% of patients hospitalised for COVID-19 pneumonia demonstrate fibrotic changes which persisted for at least 12 months after discharge (Fabbri, https://www.medrxiv.org/content/10.1101/2021.03.15.21253593v2)
- The COVID-induced atypical pneumonia and acute respiratory distress syndrome (ARDS) can cause lasting damage to the lung alveoli through irreversible scarring or fibrosis. This may lead to long-term breathing problems as well as the development of pulmonary fibrosis (https://www.immunology.org/coronavirus/immunology-and-covid-19/report-long-term-immunological-health-consequences-covid-19).
- Pulmonary fibrosis with more than 5% affected lung parenchyma were found in 21% of patients (Froidure A, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med. 2021 May;181:106383).

‘Ground glass opacity’ on CT scanning

- Ground glass opacity is the hazy gray area that can be observed in CT scans or X-rays of the lungs. These gray areas indicate increased density inside the lungs, usually caused by infection or inflammation.
- Ground-glass opacity in COVID-19 patients is common on CT scan. In previously hospitalised patients followed up after 6 months, up to 56% of patients still had persistent oxygen diffusion abnormalities on pulmonary function testing that corresponded to pulmonary interstitial changes (eg, ground glass opacities and irregular pleural lines) (Wang Y, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. Radiology. 2020 Aug;296(2):E55-E64; Huang L, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021 Aug 28;398(10302):747-758)
- A systematic review of PET/CT studies of patients with COVID-19 pneumonia showed that the most frequent findings were bilateral ground glass opacities (75%), consolidations (34.6%), and interlobar septal thickening (7.6%). (Rafiee F, et al. Coronavirus Disease 2019 (COVID-19) in Molecular Imaging: A Systematic Review of Incidental Detection of SARS-CoV-2 Pneumonia on PET Studies. Semin Nucl Med. 2021;51(2):178-191)
- These abnormalities have also been identified in CT scans of asymptomatic patients or those having mild infection (Long QX et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 26, 1200–1204 (2020)).



Anomalies in other scanning studies

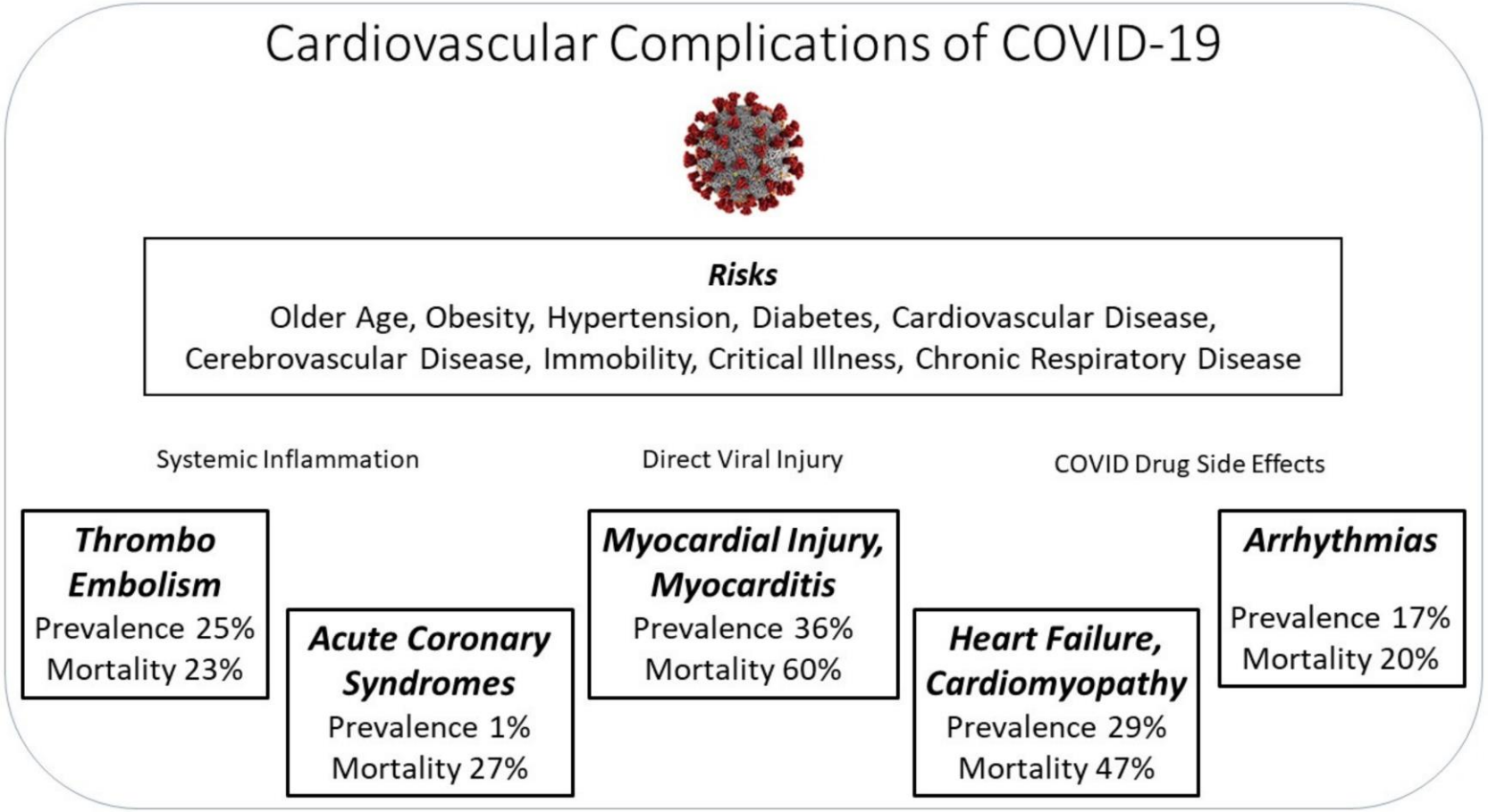
- At 6 months after acute infection, COVID-19 patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations. (Huang L, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021 Aug 28;398(10302):747-758)
- A Chinese study showed that 3 months after discharge, 71% had radiologic abnormalities consistent with pulmonary dysfunction such as interstitial thickening and evidence of fibrosis, with 25% having decreased diffusion capacity for carbon monoxide. (Zhao YM, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020 Aug;25:100463)
- Scanning was combined with exercise stress echocardiography showed a decreased O2 extraction by the exercising muscle compatible with severe deconditioning. (Naeije R, Caravita S. Phenotyping long COVID. Eur Respir J. 2021 Aug 26;58(2):2101763)
- Another study showed a significant portion of patients still had abnormal findings on chest radiography, with another 10% having deteriorating lung pathology radiologically (Mandal S, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2021 Apr;76(4):396-398).
- A follow-up of 3 months after hospital discharge found that >50% of the patients showed residual parenchymal impairment on chest CT. (Rinaldo RF, et al. Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. Eur Respir J. 2021 Aug 26;58(2):2100870)

Hypoxia

- Studies showed that at **2 month follow-up, about 6% of patients continued to require supplemental oxygen** while at a 6-month follow-up, the average 6-minute walking distance was significantly lower than the standard reference because of shortness of breath. (Chippa V, et al. Post Acute Coronavirus (COVID-19) Syndrome. 2021 Dec 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 34033370)
- Another study showed that 2 months after hospital discharge, 6.6% of patients were still using oxygen (Chopra V, et al. Sixty-Day Outcomes Among Patients Hospitalized With COVID-19. Ann Intern Med. 2021;174(4):576-578. doi:10.7326/M20-5661).
- 4 months after hospital discharge, diffusing lung capacity for carbon monoxide was reduced to less than 80% of the estimated value in 52% of patients. (Bellan M, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open. 2021 Jan 4;4(1):e2036142)
- A month after being discharged from hospital, more than 70% were reporting shortness of breath and 13.5% were still using oxygen at home. (Weerahandi H et al. Post-Discharge Health Status and Symptoms in Patients with Severe COVID-19. J GEN INTERN MED 36, 738–745 (2021))

Predictors of pulmonary dysfunction

- **Blood urea nitrogen (aka urea, a test of renal function) concentration at admission was associated with the presence of CT abnormalities at 3 months after hospital discharge and the measurement of D-dimer levels at admission predicted impaired diffusion defect** (Zhao YM, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020 Aug;25:100463)
- A Korean study found that those with **subsequent lung fibrosis had higher levels of CRP and IL-6**. The fibrosis group were older, had a longer-term of hospitalisation, longer duration of pulsed steroid therapy and antiviral therapy. (Yu M, et al. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. Korean J Radiol. 2020;21(6):746-755)
- Independent predictors of fibrosis at 6 months were age >50, heart rate >100bpm on admission to hospital, duration of hospital stay, development of ARDS, non-invasive mechanical ventilation and CT score. (Han X, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology. 2021;299(1):E177-E186)
- The numbers of days in intensive care units were related to the extent of lesions on CT scans, and intubation was associated with signs of fibrosis. In contrast, the severity of lung problems were not predictive of fatigue and dyspnoea. (Froidure A, et al. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med. 2021 May;181:106383)
- The predictors of pulmonary fibrosis in COVID-19 infection are advanced age, illness severity, length of ICU stay and mechanical ventilation, smoking and chronic alcoholism. (Ojo AS, et al. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med. 2020;2020:6175964)



(Lee CCE, et al. COVID-19-Associated Cardiovascular Complications. Diseases. 2021 Jun 29;9(3):47)

Cardiovascular disease (CVD) in Long COVID: Summary

- COVID-19 may either induce **new cardiac pathology or exacerbate pre-existing CVD**.
- **Symptoms show no relationship to original COVID-19 severity**.
- There is an **increased risk of major CV events** (heart failure, myocardial infarction, stroke, venous or pulmonary thromboembolism) **up to at least 5 months after infection. Risk of death is high within the first month**.
- Biomarkers indicate **elevated inflammation (CRP and IL-6) and clotting (D-dimer and other markers of coagulation) up to 4 months after infection**.
- Imaging studies show myocardial inflammation (myocarditis and pericarditis) persisting at 2 months after infection and may correlate with troponin and inflammatory markers.
- Cardiac MRI also shows abnormalities in up to 78% of patients, with electrocardiographic abnormalities in up to 50%.

Cardiovascular disease (CVD): main symptoms and developments

- COVID-19 may either induce new cardiac pathologies and/or exacerbate underlying cardiovascular diseases. (Madjid M, et al. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol. 2020 Jul 1;5(7):831-840)
- The most common cardiovascular (CV) symptoms present in long COVID are chest pain/tightness, tachycardia (palpitations), dizziness and an increase in resting heart rate. These symptoms appear in both hospitalised and non-hospitalised patients and there is no clear relationship with CV symptoms and pre-existing CV disease. Other potential developments include hypercoagulability, microangiopathy, thromboembolism, myocarditis, pericarditis, microvascular injury causing impaired myocardial flow reserve, coronary artery or aortic aneurysm, myocardial infarction, accelerated atherosclerosis, atrial fibrillation, complete heart block, life-threatening arrhythmias and sudden cardiac death. (Dixit NM, et al. Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known? Am Heart J Plus. 2021 May;5:100025; Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811; Yan Z, et al. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines. 2021;9(8):966; Raveendran AV, et al. Long COVID: An overview. Diabetes Metab Syndr. 2021;15(3):869-875)
- Significant cardiac complications after COVID-19 recovery may occur even in patients with mild acute symptoms, home-based recovery and no pre-existing cardiovascular conditions. These may include new signs of heart failure, chest pain, palpitations, weakness, shortness of breath or cough. (Ramakrishnan RK, et al. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. Front Immunol. 2021;12:686029; Richter D, et al. Late phase of COVID-19 pandemic in General Cardiology. A position paper of the ESC Council for Cardiology Practice. ESC Heart Fail. 2021 Oct;8(5):3483-3494)

CVD prevalence and duration

- In a high quality UK study with matched control groups there was a **3 times higher risk of developing heart failure, myocardial infarction, stroke and arrhythmia at 5 months** after hospital discharge in the COVID-19 cohort, compared with matched controls (Ayoubkhani D, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021 Mar 31;372:n693).
- Beyond the first 30 days after infection, individuals with COVID-19 are at **increased risk of cardiovascular disease**, including cerebrovascular disorders, dysrhythmias, ischaemic and non-ischaemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease **for at least 1 year**. This risk was evident **even among individuals who were not hospitalised during the acute phase of the infection but risk increased with degree of severity of the infection**. (Xie Y, et al. Long-term cardiovascular outcomes of COVID-19. Nat Med (2022))
- Approximately 20% of individuals reported chest pain and 14% reported palpitations at 2 months after COVID-19 (Chilazi M, et al. COVID and Cardiovascular Disease: What We Know in 2021. Curr Atheroscler Rep. 2021;23(7):37. Published 2021 May 13).
- Several studies found that more than 50% of patients still complain of cardiac symptoms many weeks post-COVID-19. (Ramadan MS, et al. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. Clin Microbiol Infect. 2021;27(9):1250-1261)
- Studies are variously reporting chest pain and palpitations at 6 months (Nalbandian A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615)

Arrhythmia

- Arrhythmia has been associated with acute COVID-19, especially in critically ill patients and those treated with arrhythmogenic and QT prolonging medications such as azithromycin. (Dherange P, et al, Arrhythmias and COVID-19: a review, JACC; Clin. Electrophysiol. 6 (9) (Sep 2020) 1193–1204)
- A wide range of arrhythmias has been reported to complicate the course of COVID-19 including potential pro-arrhythmic effects of medical treatment targeted at COVID-19 used during the first months of pandemic (Giustino G, et al. Coronavirus and Cardiovascular Disease, Myocardial Injury, and Arrhythmia: JACC Focus Seminar. J Am Coll Cardiol. 2020;76(17):2011-2023).

Vascular problems: blood clots

- COVID-19 can make blood cells more likely to clump and form clots. While large clots can cause heart attacks and strokes, much of the heart damage caused by COVID-19 is believed to stem from very small clots that block tiny blood vessels (capillaries) in the heart muscle. Other parts of the body affected by blood clots include the lungs, legs, liver and kidneys. COVID-19 can also weaken blood vessels and cause them to leak, which contributes to potentially long-lasting problems with the liver and kidneys.
- The blood clots seen in some COVID-19 patients persist for several weeks after recovery from acute infection, possibly due to injured blood vessel cells, overactive platelets or errant immune cells. The persistence of these clots in long COVID patients could eventually cause fibrosis of different organs and explain many of the symptoms experienced by this group of patients.
- Blood clots in particular have received a lot of attention as a possible driver of long COVID, in large part because of the growing body of evidence that acute SARS-CoV-2 infection could trigger cell signalling events that lead to clot formation. A recent review even argued that COVID-19 should be treated as a disease of the vascular endothelium and not as a respiratory disease.
- Disproportionate activation of the complement system can lead to excessive coagulation in the blood and thrombotic complications, pulmonary embolism, cardiac injury and stroke.

(https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-long-term-effects/art-20490351; https://www.immunology.org/coronavirus/immunology-and-covid-19/report-long-term-immunological-health-consequences-covid-19; https://www.the-scientist.com/features/mechanisms-of-long-covid-remain-unknown-but-data-are-rolling-in-69066)

Vascular problems: thromboembolic events

- Studies from the UK have shown **there was a rate of venous thromboembolism of up to 2.6% at 1-2 months**. (Roberts LN, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. Blood 2020; 136 (11):1347–50; Salisbury R, et al. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. Blood Adv 2020; 4 (24):6230–9)
- At 4 months post discharge, patients had elevated plasma levels of factor VIII and plasminogen-activator inhibitor type 1, indicating enhanced thrombin-generating capacity and decreased plasma fibrinolytic potential. (von Meijenfeldt FA, et al. Sustained prothrombotic changes in COVID-19 patients 4 months after hospital discharge. Blood Adv 2021; 5 (3):756–9107)
- Thromboembolic events during acute COVID-19 can lead to persistent pathology after recovery. The incidence of venous thromboembolism is 0.48% to 0.6% and is most likely in patients who were transferred to intensive care. (Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811)
- In a study of hospitalised COVID-19 patients, 2.5% of patients followed for up to 1 month after discharge experienced some form of thrombotic event (segmental pulmonary embolism, intracardiac thrombus, thrombosed arteriovenous fistula, and/or ischaemic stroke), with 0.7% experiencing a major haemorrhage. (Patell R, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. Blood. 2020 Sep 10;136(11):1342-1346)
- Agents used in acute COVID-19, such as tocilizumab, can result in thrombosis, even after the resolution of the acute infection. (Atallah B, et al. Thrombotic events following tocilizumab therapy in critically ill COVID-19 patients: a Facade for prognostic markers. Thromb J 2020; 18 :22)

CVD mortality

- The post-discharge mortality rate of COVID-19 survivors with cardiovascular comorbidities remain high. In a multicentre study including over 4000 patients in Poland, an overall **post-discharge mortality rate of patients with cardiovascular co-morbidities was 42%.**
- The median time to death after discharge was 14 (range 7–30) days. At 2 months after discharge, an additional 5% of the whole study cohort died.

(Gąsior M, et al. High postdischarge mortality in hospitalized COVID-19 patients with cardiovascular comorbidities. Pol Arch Intern Med. 2021 Aug 30;131(7-8):749-751)

CVD imaging studies: inflammation

- Cardiac magnetic resonance imaging **2-3 months after diagnosis revealed ongoing myocardial inflammation in 60% of patients**, which was independent of pre-existing conditions, severity and overall course of the acute illness, and the time from the original diagnosis. These German patients were relatively young and healthy – the average age was 49, and many had not needed hospitalisation for COVID-19. Endomyocardial biopsy in patients with severe findings revealed active lymphocytic inflammation. (Puntmann VO, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Nov 1;5(11):1265-1273)
- In a study of 26 competitive college athletes with mild or asymptomatic infection, cardiac MRI revealed features diagnostic of myocarditis in 15% of participants, and previous myocardial injury in 30.8% of participants. Others have shown a high prevalence of imaging abnormalities suggestive of myocardial injury and inflammation in myocarditis. (Rajpal S, et al. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. JAMA Cardiol. 2021 Jan 1;6(1):116-118; Dixit NM, et al. Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known? Am Heart J Plus. 2021 May;5:100025)

Myocarditis and pericarditis

- Myocarditis is a known complication of many acute viral infections and is a disease of the heart characterized by inflammatory infiltrates and myocardial injury without an ischaemic cause; it is the cause of death in some COVID-19 patients and carries a risk of arrhythmia as well as progression to heart failure and cardiogenic shock.
- The pathophysiology of COVID-19–related myocarditis is thought to be a combination of direct cell injury and T-lymphocyte–mediated cytotoxicity, which can be augmented by the cytokine storm. Interleukin 6 (IL-6) seems to be the central mediator of the cytokine storm, in which it orchestrates the proinflammatory responses from immune cells, including the T lymphocytes. This process causes T-lymphocyte activation and a further release of inflammatory cytokines, which stimulate more T lymphocytes, leading to a positive feedback loop of immune activation and myocardial damage.
- The long-term effects of healed myocarditis are completely unknown. In a study of patients with active and healed myocarditis, monomorphic ventricular tachycardia and regular ventricular arrhythmias were more frequent in those with healed than acute myocarditis.
- Pericarditis is swelling and irritation of the thin, saclike tissue surrounding the heart (pericardium). Pericarditis often causes sharp chest pain, which occurs when the irritated layers of the pericardium rub against each other. Pericarditis is usually mild and goes away without treatment. Treatment for more-severe cases may include medications and, rarely, surgery.
- Possible mechanisms include priming of T-lymphocytes by the spike protein, which migrate to cardiomyocytes and cause myocardial inflammation through cell-mediated cytotoxicity. In the cytokine storm, in which proinflammatory cytokines are released into the circulation, T-lymphocyte activation is augmented and releases more cytokines. This results in a positive feedback loop of immune activation and myocardial damage.

(Siripanthong B, et al. Recognizing COVID-19-related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020;17(9):1463-1471; https://www.mayoclinic.org/diseases-conditions/pericarditis/symptoms-causes/syc-20352510; Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811)

Prevalence of myocarditis and pericarditis in Long COVID

- **Myocarditis was diagnosed in 26% of patients, pericarditis was in 3% and myopericarditis in 11%.** Pericarditis was associated with elevated immune cell numbers, while participants diagnosed with myopericarditis or myocarditis had lower plasmacytoid dendritic cell, NK-cell and plasma cell counts and lower anti-SARS-CoV-2-IgG antibody levels. (Eiros https://www.medrxiv.org/content/10.1101/2020.07.12.20151316v1)
- Myocardial inflammation or scarring is found in significant number of patients, even those who were asymptomatic or experienced only mild symptoms of acute disease. These findings were correlated with troponin levels and inflammatory markers such as CRP, white cell count and procalcitonin, indicating a role of inflammation in myocardial tissue abnormalities. Myocardial fibrosis or scarring and resultant cardiomyopathy can lead to arrhythmias. (Korompoki E, et al. Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021;83(1):1-16; Liu PP, et al. The science underlying COVID-19: implications for the cardiovascular system. Circulation. 2020; 142, 68–78)
- Myocarditis was reported in groups with asymptomatic/mild COVID-19, and in healthy populations such as athletes, but without evidence of a greater arrythmia risk. (Ramadan MS, et al. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. Clin Microbiol Infect. 2021;27(9):1250-1261)
- Myocarditis was also found in an 11-year old child who died as a result. (Dolhnikoff M, et al. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. Lancet Child Adolesc Health. 2020 Oct;4(10):790-794)

CVD imaging studies: cardiac abnormalities

- Imaging 2-3 months after diagnosis revealed cardiac abnormalities in 29%-78% of patients, which was independent of pre-existing conditions, severity and overall course of the acute illness, and the time from the original diagnosis. Compared with healthy controls and risk factor–matched controls, the patients had lower left ventricular ejection fraction, higher left ventricle volumes, pericardial effusion (15%) and raised native T1 (30%) and T2 (16%). There were electrocardiographic abnormalities in 50%, NT-pro-BNP was elevated in 8%; troponin in 1%. Studies showed abnormal signal changes on STIR sequence and 11% with late gadolinium enhancement (LGE) suggestive of oedema and myocardial fibrosis/scarring. The basal and mid, inferior, and inferolateral segments were the common sites of LGE reported in the study. 9% of patients had X- rays showing deterioration seven to eight weeks after discharge from hospital.
- Between 3-6 months, common changes included reduced left ventricular global longitudinal strain (30%) and late gadolinium enhancement (10%) on CMR, diastolic dysfunction (40%) on echocardiography and elevated N-terminal proB-type natriuretic peptide (18%). In addition, COVID-19 survivors had higher risk of developing heart failure, arrythmias and myocardial infarction. There was a very high rate of reported symptoms of cardiac disease, mostly chest pain and palpitations, despite decreasing evidence on imaging.

(Ramadan MS, et al. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. Clin Microbiol Infect. 2021;27(9):1250-1261; Leviner S. Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers. J Nurse Pract. 2021;17(8):946-949; Puntmann VO, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Nov 1;5(11):1265-1273; Eiros, https://www.medrxiv.org/content/10.1101/2020.07.12.20151316v1; Huang L, et alL. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. JACC Cardiovasc Imaging. 2020 Nov;13(11):2330-2339; Wang H et al. Cardiac involvement in COVID-19 patients: mid-term follow up by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 23, 14 (2021); Mandal S, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2021;76(4):396-398; Ramadan MS, et al. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. Clin Microbiol Infect. 2021;27(9):1250-1261; Richter D, et al. Late phase of COVID-19 pandemic in General Cardiology. A position paper of the ESC Council for Cardiology Practice. ESC Heart Fail. 2021 Oct;8(5):3483-3494; Moody WE, et al. Persisting Adverse Ventricular Remodeling in COVID-19 Survivors: A Longitudinal Echocardiographic Study. J Am Soc Echocardiogr. 2021;34(5):562-566)

Biomarkers

- **2 months after hospital discharge, 30% of people had persistently elevated D–dimer levels (indicating clotting) and 10% had raised levels of C-reactive protein (CRP), which measures inflammation.** (Mandal S, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2021;76(4):396-398)
- 17% of patients followed up after hospital discharge had D-dimer values twice the threshold for diagnosis of pulmonary embolism three months after they first tested positive for Covid-19. (Venturelli S, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. Epidemiol Infect. 2021 Jan 19;149:e32)
- Increased D-dimer levels (>500 ng/ml) were observed in 25% of patients up to 4 months post-SARS-CoV-2 infection; 29% of patients with elevated convalescent D-dimer had been managed exclusively as out-patients during their illness. In contrast, other markers of coagulation (prothrombin time, activated partial thromboplastin time, fibrinogen, platelet count) and inflammation (CRP and IL-6) had returned to normal in >90% of convalescent patients at a median of 80.5 days (Townsend L, et al. Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. J Thromb Haemost. 2021 Apr;19(4):1064-1070).
- Severe systemic inflammation in patients with SARS-CoV-2 is one of the causes of myocardial injury. High levels of circulating cytokines and mediators of toxic response have been described, including IL-6, TNF-, nitric oxide and activity modulation of the calcium channel. These may generate myocardial depression in systemic hyperinflammatory states, including sepsis. (Silva Andrade B, et al. Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms. Viruses. 2021 Apr 18;13(4):700)

Common persisting gut symptoms and prevalence

- Among patients hospitalised for COVID-19, up to 44% reported gastrointestinal symptoms 3 months after discharge. Loss of appetite (24%), nausea (18%), acid reflux (18%) and diarrhoea (15%) were the most commonly reported gastrointestinal symptoms. (Weng J, et al. Gastrointestinal sequelae 90 days after discharge for COVID-19. Lancet Gastroenterol Hepatol. 2021 May;6(5):344-346).
- Some symptoms, such as loss of appetite, diarrhoea, and vomiting, persisted 6 months after hospital discharge (Huang C, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220-232).
- Studies have found that the prevalence of persistent symptoms is loss of appetite (8%-24%), nausea (18%), acid reflux (18%), and diarrhoea (5%-15%), abdominal distension (14%), belching (10%), vomiting (9%), abdominal pain (7%), and bloody stools (2%) (Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811).

Microbiome alterations

- A Chinese study investigated the microbiome content in hospitalised patients and found a **COVID-19 specific composition of gut microbiota**; the amount of Coprobacilli, Clostridium ramosum, and Clostridium hathewayi at baseline correlated positively with COVID-19 severity. The amount of Faecalibacterium prausnitzii, an anti-inflammatory bacterium, correlated inversely with disease severity. Also, the presence of Bacteroides dorei, Bacteroides thetaiotaomicron, Bacteroides massiliensis, and Bacteroides ovatus, the bacteria downregulating expression of ACE2 in murine models, correlated inversely with SARS-CoV-2 vial shedding in stool. (Zuo T, et al. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. Gastroenterology. 2020;159(3):944-955.e8)
- We can see this reflected up to 30 days after disease resolution, when several gut commensals with known immunomodulatory potential such as Faecalibacterium prausnitzii, Eubacterium rectale and bifidobacteria were underrepresented in patients and remained low. Moreover, this perturbed composition correlated with disease severity and concentrations of inflammatory cytokines and blood markers such as C reactive protein, lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase. (Yeoh YK, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021 Apr;70(4):698-706)

Prevalence of acute kidney injury with need for renal replacement therapy

- Acute kidney injury (AKI) is a common complication of acute COVID-19 disease, **affecting up to 37% of hospitalised patients**, some requiring renal replacement therapy (RRT) [dialysis is a form of RRT]. Kidney function does recover among most survivors, even among those with stage 3 AKI. Among patients requiring RRT in the hospital, 20% to 34% remain dependent on RRT after hospital discharge, and among those still alive more than 60 days after discharge, >56% remained RRT-dependent. (Jiang DH, McCoy RG. Planning for the Post-COVID Syndrome: How Payers Can Mitigate Long-Term Complications of the Pandemic. J Gen Intern Med. 2020;35(10):3036-3039)
- AKI, both with and without need for RRT, was significantly associated with risk of death. Among discharged patients with AKI who required RRT in hospital, 31% remained on dialysis at the time of discharge. Among patients with AKI who did not require RRT, 37% continued to have kidney dysfunction at the time of hospital discharge. (Ng JH, et al. Outcomes Among Patients Hospitalized With COVID-19 and Acute Kidney Injury. Am J Kidney Dis. 2021 Feb;77(2):204-215.e1)
- Among discharged survivors with AKI, one in three would still depend on renal replacement therapy (RRT) at discharge, and one in six remains RRT dependent 60 days after hospital admission (Gupta S, et al. AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19. J Am Soc Nephrol. 2021 Jan;32(1):161-176).

Acute kidney injury: eGFR and outcomes

- Among hospitalised patients with AKI during acute COVID-19, **decreased estimated glomerular filtration rate (eGFR) was reported in 35% at 6 months follow-up**. Among hospitalised patients without AKI and with normal estimated glomerular filtration rate (eGFR) at the acute phase, 13% had decreased eGFR at follow-up. (Huang C, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220-232)
- **1.4% of patients experienced renal failure in longer term follow-up** of Long COVID-19 Syndrome (Kamal M, et al. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract. 2021 Mar;75(3):e13746).
- Longer follow-up duration shows more promising results for restoration of renal functions in survivors with previous AKI: after 5 months, over 90% achieve variable degrees of renal recovery, with over 60% achieving complete recovery (Stockman, https://www.kidney-international.org/article/S0085-2538(21)00069-7/fulltext).
- SARS-CoV-2 has been isolated from renal tissue, and renal biopsies and autopsies show acute tubular necrosis as the primary finding. COVID-19-associated nephropathy (COVAN) is characterised by the collapsing variant of focal segmental glomerulosclerosis, with involution of the glomerular tuft in addition to acute tubular injury, and is thought to develop in response to interferon and chemokine activation. Thrombi in the renal microcirculation may also potentially contribute to the development of renal injury. (Nalbandian A et al. Post-acute COVID-19 syndrome. Nat Med 27, 601–615 (2021))

Liver: biomarkers and scanning

- At 2 week follow-up, previously hospitalised COVID patients, some with pre-existing liver disease, showed elevation of aspartate transferase (AST) and alanine transferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) but **at 2 month follow-up, the liver enzymes had generally normalised**. The side effects of COVID-19 drugs may be one of the primary causes of liver damage in long COVID patients (An YW, et al. Liver function recovery of COVID-19 patients after discharge, a follow-up study. Int J Med Sci 2021; 18(1):176-186)
- **At 2–3 months from disease-onset, MRI abnormalities such as fibro-inflammation were seen in the liver in 10% of patients**. (Raman B, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine. 2021 Jan 7;31:100683)
- 10% of low risk young patients showed mild liver impairment 4-5 months after COVID-19 (Dennis, https://www.medrxiv.org/content/10.1101/2020.10.14.20212555v1).

Pancreatic injury

- **In low-risk young patients at 4-5 months after infection, 17% showed evidence of mild pancreatic impairment** (Dennis A, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. BMJ Open. 2021 Mar 30;11(3):e048391).
- Long COVID patients may suffer from **pancreatitis**, possibly in conjunction with hepatitis (Leviner S. Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers. J Nurse Pract. 2021;17(8):946-949).
- Pancreatic injury was seen in 17% of hospitalised COVID-19 patients and was often accompanied by loss of appetite and diarrhoea, lower levels of $CD3^+$ and $CD4^+$ T cells and higher levels of aspartate aminotransferase, γ-glutamyltransferase, creatinine, lactate dehydrogenase and erythrocyte sedimentation rate. (Wang F, et al. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. Gastroenterology. 2020 Jul;159(1):367-370)
- 1-2% of non-severe and 17% of severe COVID-19 patients had pancreatic injury. ACE2 is expressed in both exocrine glands and islets of the pancreas and this expression was slightly higher than in the lungs, suggesting that SARS-CoV-2 might bind to ACE2 in the pancreas and cause pancreatic injury. (Liu F, et al. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol. 2020;18(9):2128-2130.e2)
- SARS-CoV-2-associated microvascular injury may cause perfusion abnormalities within the pancreatic islets. In the islet, for example, microcirculation is essential for both glucose sensing and insulin secretion; abnormal islet capillary architecture and fragmentation contributes to beta cell dysfunction in type 1 and type 2 diabetes. (Rando, https://www.medrxiv.org/content/10.1101/2021.03.20.21253896v1)

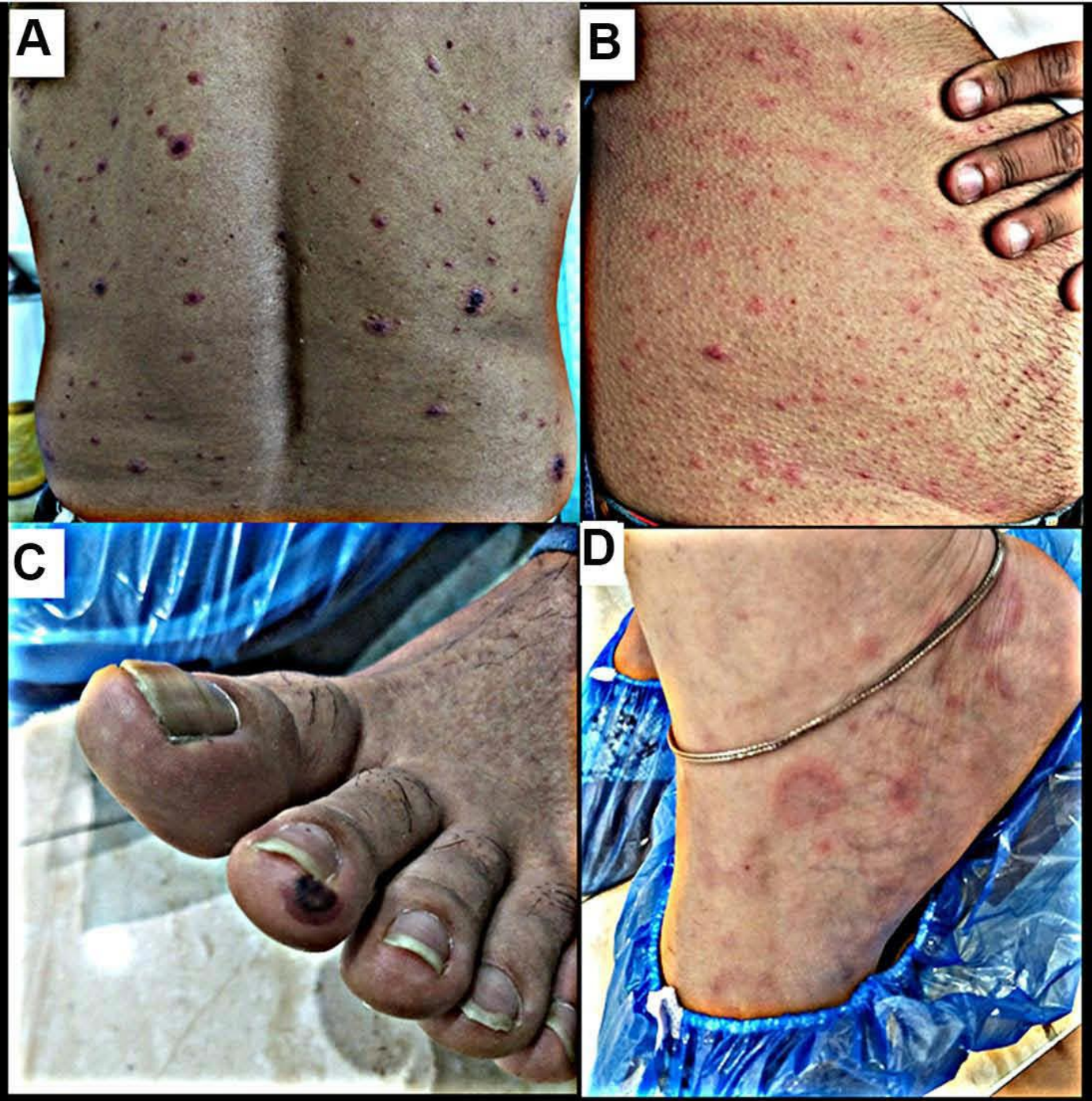
Spleen

- A cross sectional study found mild impairment of the spleen in 4% of those assessed at 4-5 months following clearance of COVID-19. (Dennis, https://www.medrxiv.org/content/10.1101/2020.10.14.20212555v1?ijkey=7b44ea7e93baedb6080ecd8ce230674729411ab6&keytype2=tf_ipsecsha)

Skin manifestations

- An international registry for COVID-19 dermatological manifestations has reported morbilliform rashes, urticarial eruptions, and papulo-squamous lesions. Urticarial and morbilliform rashes are short lasting, whereas the chilblain-like lesions (pernio) and livedo-reticularis lasted for more than 2 months. (McMahon DE, et al. Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. Lancet Infect Dis. 2021;21(3):313-314)
- Skin lesions may develop up to 2 weeks after acute COVID-19 infection. The most common cutaneous manifestations of COVID-19 were maculopapular exanthem (morbilliform), presenting in 36% of patients, papulovesicular rash (35%), urticaria (10%), painful acral red purple papules (15%), livedo reticularis lesions (3%) and petechiae (1%). The majority of lesions were localised on the trunk (67%), however, 19% of patients experienced cutaneous manifestations in the hands and feet. The majority of studies reported no correlation between COVID-19 severity and skin lesions. (Sachdeva M, et al. Cutaneous manifestations of COVID-19: Report of three cases and a review of literature. J Dermatol Sci. 2020 May;98(2):75-81)
- The most common manifestations were morbilliform (22%), pernio-like (18%), urticarial (16%), macular erythema (13%), vesicular (11%), papulosquamous (10%) and retiform purpura (6%). Pernio-like lesions were common in patients with mild disease, whereas retiform purpura presented exclusively in ill, hospitalized patients. 64% of dermatologic manifestations of COVID-19 occurred after the acute COVID-19 symptoms (Freeman EE, et al. The spectrum of COVID-19-associated dermatologic manifestations: An international registry of 716 patients from 31 countries. J Am Acad Dermatol. 2020;83(4):1118-1129). Skin lesions normally resolved within 2 to 8 weeks (https://www.uptodate.com/contents/covid-19-cutaneous-manifestations-and-issues-related-to-dermatologic-care)

Garg, https://pubmed.ncbi.nlm.nih.gov/34163217/



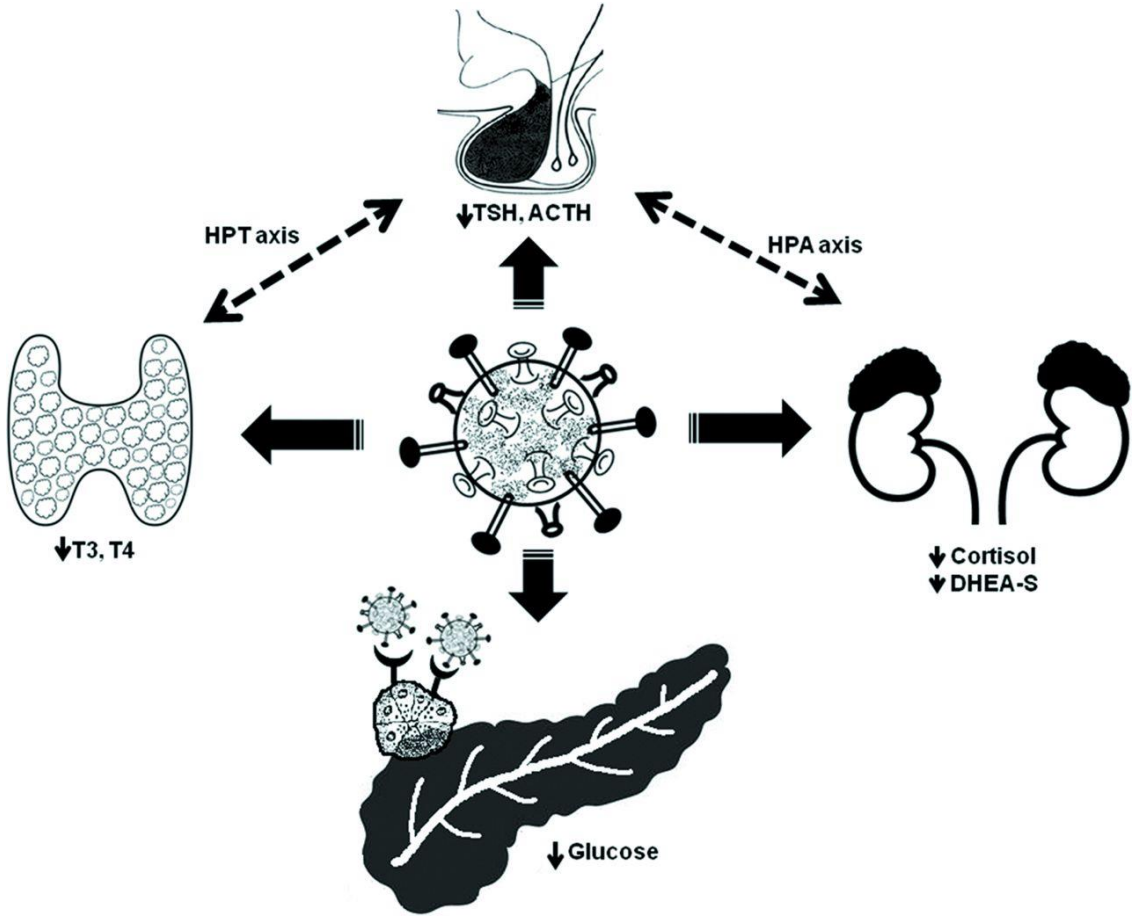
(A) Haemorrhagic guttate psoriatic lesions on the back in previously known psoriasis patient (5 weeks after symptom onset)
(B) Retiform maculopapular itchy rash on the trunk (10 weeks after disease onset)
(C) Persistent, asymptomatic COVID toe (12 weeks after initial diagnosis)
(D) Erythema multiforme lesions on the right foot (6 weeks following symptom onset).

Common musculoskeletal symptoms

- **Myalgias and arthralgias** are common complaints in Long COVID. (Leviner S. Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers. The journal for nurse practitioners: JNP vol. 17,8 (2021): 946-949)
- **Sarcopenia (loss of muscle mass and function) through prolonged hospital stay** is also common; sufferers will likely require some form of rehabilitation to regain lost muscle mass and function. The SARS-CoV-2 hyperinflammation exacerbates the immuno-senescence process, enhances endothelial damage and induces myofibrillar breakdown and muscle degradation. This is exacerbated by imposed physical inactivity, lockdown, quarantine and stress which has led to poor diet (snacks instead of protein) as well as inactivity. (Piotrowicz K et al. Post-COVID-19 acute sarcopenia: physiopathology and management. Aging clinical and experimental research vol. 33,10 (2021): 2887-2898; Kirwan R, et al. Sarcopenia during COVID-19 lockdown restrictions: long-term health effects of short-term muscle loss. Geroscience. 2020;42(6):1547–1578)
- COVID-19 survivors may experience detrimental effects on bone and muscle health. Steroid therapy, critical illness, and decreased mobility all contribute to bone loss and sarcopenia. (Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811)

Endocrine system

Schematic representing endocrine changes seen in SARS-CoV infections.



Key: ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; HPA, hypothalamic–pituitary–adrenal; HPT, hypothalamo–pituitary–thyroid; SARS-CoV, severe acute respiratory syndrome coronavirus; TSH, thyroid stimulating hormone.

(Agarwal S, Agarwal SK
Endocrine changes in SARS-CoV-2 patients and lessons from SARS-CoV. Postgraduate Medical Journal 2020;96:412-416)

Endocrine system

- ACE2 receptors are expressed in the hypothalamus, pituitary, adrenal gland, thyroid, testes, and pancreatic islets leading to the involvement of the endocrine system during and after the recovery of the disease. (Bansal R, et al. COVID-19 and chronic fatigue syndrome: An endocrine perspective. J Clin Transl Endocrinol. 2022 Mar;27:100284)
- Despite this, there are **very few studies on Long COVID and endocrine function**. Most concern thyroid and pancreas (for diabetes).

Thyroid

- **At 3 months after acute COVID-19, most abnormal thyroid function tests had resolved and thyroid dysfunction was rare.** Nonetheless, antithyroid peroxidase (anti-TPO) positivity was seen in some and Long COVID symptom resolution was more likely in those with positive anti-TPO upon follow-up. (Lui DTW, et al. Long COVID in Patients With Mild to Moderate Disease: Do Thyroid Function and Autoimmunity Play a Role? Endocr Pract. 2021 Sep;27(9):894-902)
- SARS-CoV-2 may lead to thyroid injury and dysfunction, with cases of several subclinical and atypical thyroiditis being described in infected patients, usually a few weeks after diagnosis. The clinical course is usually short and uncomplicated. Some cases of autoimmune thyroiditis have also been reported. (Lisco G, et al. COVID-19 and the Endocrine System: A Comprehensive Review on the Theme. J Clin Med. 2021 Jun 29;10(13):2920)
- In another observational cohort study on COVID-19 patients, 87% of COVID-19 patients were euthyroid on admission. During COVID-19 they experienced thyroid deficiency but on follow-up ar 2-3 months, most patients became euthyroid again, however, the study did not follow-up patients for symptoms of long COVID (Khoo B, et al. Thyroid Function Before, During, and After COVID-19. J Clin Endocrinol Metab. 2021;106(2):e803-e11).
- Subacute thyroiditis with clinical thyrotoxicosis has been reported weeks after the resolution of respiratory symptoms. COVID- 19 may also potentiate latent thyroid autoimmunity manifesting as new-onset Hashimoto's thyroiditis or Graves' disease. (Nalbandian A et al. Post-acute COVID-19 syndrome. Nat Med; 2021: 27, 601–615)
- Thyroid dysfunction has been detected in 15–20% of patients with COVID-19. As the thyroid is closely linked to T-cell-mediated autoimmunity, thyroid dysfunction may play a role in the autoimmunity pathophysiology of long COVID. (Lui DTW, et al. Thyroid dysfunction in relation to immune profile, disease status and outcome in 191 patients with COVID-19. J Clin Endocrinol Metab. 2020;106(2):e926–e935; Muller I, et al. SARS-CoV-2-related atypical thyroiditis. The Lancet Diabetes & Endocrinology. 2020;8(9):739–741)

Diabetes

- The ACE2 receptor is strongly expressed in pancreatic endocrine tissue (Yang JK, et al. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47: 193–199), predisposing patients to islet cell injury and diabetes.
- Although new onset diabetes has been found in some patients, COVID-19 may have unmasked existing diabetes by aggravating its metabolic complications rather than causing new-onset disease in these patients. Diabetic ketoacidosis has been observed in patients without known diabetes mellitus weeks to months after resolution of COVID-19 symptoms. (Suwanwongse K, Shabarek N. Newly diagnosed diabetes mellitus, DKA, and COVID-19: Causality or coincidence? A report of three cases. J Med Virol. 2021 Feb;93(2):1150-1153).
- There is no concrete evidence of lasting damage to pancreatic β cells (Gentile S, et al. COVID-19, ketoacidosis and new-onset diabetes: Are there possible cause and effect relationships among them?. Diabetes Obes Metab. 2020;22(12):2507-2508).
- Some patients may develop diabetic ketoacidosis, regardless of whether there was pre-existing diabetes (Alsadhan I, et al. Diabetic ketoacidosis precipitated by coronavirus disease 2019 infection: case series. Curr Ther Res Clin Exp. 2020;93:100609)
- Patients may present with severe or mild hyperglycaemia. Patients with more severe manifestations of acute COVID-19 appear to be at higher risk of new onset diabetes, with a correlation between hypoxia and hyperglycaemia among hospitalised patients without pre-existing diabetes and prior to administration of glucocorticoid therapy. (Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811)

Principal neurological symptoms and conditions

- Impaired or loss of consciousness
- Loss of smell and taste (anosmia and ageusia)
- Headaches
- Brain fog: lack of concentration, attention deficit, difficulty in task planning, confusion, short-term memory impairment, dizziness
- Changes in behaviour
- Spasms, convulsions,
- Visual impairment,
- Myalgia, weakness, pain, Peripheral neuropathies
- Tinnitus, vertigo, hearing loss, earache
- Ataxia (a group of disorders that affect co-ordination, balance and speech)
- Numbness, tingling, pins-and-needles sensation
- Insomnia
- Hemiplegia (caused by a brain injury, that results in a varying degree of weakness, stiffness and lack of control in one side of the body)
- Guillain-Barré syndrome, a rare, autoimmune disorder in which one's own immune system damages the peripheral nerves, causing muscle weakness and sometimes paralysis; can be life-threatening.
- Miller-Fisher syndrome, a rare, acquired nerve disease that is considered to be a variant of Guillain-Barré syndrome. It is characterized by abnormal muscle coordination, paralysis of the eye muscles, and absence of the tendon reflexes.
- Encephalitis, encephalopathy, seizures, stroke, cerebral vasculitis, haemorrhage, dementia, autoimmune acute demyelinating encephalomyelitis, myoclonus, myositis, acute transverse myelitis, poorly organized motor tasks, and disorientation

(https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/how-does-coronavirus-affect-the-brain; Silva Andrade B, et al. Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms. Viruses. 2021 Apr 18;13(4):700; Garg M, et al. The Conundrum of 'Long-COVID-19': A Narrative Review. Int J Gen Med. 2021 Jun 14;14:2491-2506; Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811; Korompoki E, et al. Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021 Jul;83(1):1-16.

Neurological condition prevalence: many studies (this is a small selection)

- A systematic review found that nearly 15% of those who recovered from COVID-19 experienced tinnitus; about 8% reported hearing loss; and more than 7% developed rotatory vertigo, which causes dizziness similar to being on a merry-go-round. (Almufarrij I, Munro KJ. One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms. Int J Audiol. 2021 Dec;60(12):935-945)
- Loss of smell and taste may affect up to 37% and 7% of patients respectively at 5 weeks post-hospital discharge. (Le Bon SD et al. Psychophysical evaluation of chemosensory functions 5 weeks after olfactory loss due to COVID-19: a prospective cohort study on 72 patients. Eur Arch Otorhinolaryngol 2020;278:101–108)
- A large study showed that the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months post COVID-19 was approximately 34%, with 13% of patients with new onset disorders. The estimated incidence was around 46% for severely ill patients admitted to ICU, with 26% for a first diagnosis. Among those who had been admitted to intensive care with severe COVID-19, 7% had a stroke within six months and almost 2% were diagnosed with dementia. (Taquet M., et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021)
- The international patient-led study of Long COVID symptoms recorded self-reported brain fog or cognitive dysfunction in 85% of respondents, with poor concentration (75%), memory impairment (73%) and difficulty thinking (65%). Cognitive dysfunction increased over the first 3 months and was present in all age groups. (Davis et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:1010192020)
- After more than 3 months after hospital discharge patients complained of fatigue (55%), dyspnoea (42%), loss of memory (34%) loss of concentration (28%), sleep disorders (30.8%). (Garrigues, E et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J. Infect. 2020, 81, e4–e6)
- A study of hospitalized patients found that the most frequent neurologic manifestations were myalgias (44.8%), headaches (37.7%), encephalopathy (31.8%), dizziness (29.7%), altered smell (11.4%) and taste (15.9%)) with between 0.2 and 1.4% of hospitalized patients suffering from strokes, movement disorders, motor and sensory deficits, ataxia and seizures. (Liotta EM et al. (2020). Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol.7(11):2221–30)

Neurological conditions: brain scanning studies

- **PET scans of the brains of Long Covid sufferers >3 weeks after initial infection showed biomarkers consistent with memory and cognitive impairment and autonomic dysfunction. There was significant hypometabolism in the brain**, including the olfactory gyrus, right temporal lobe (hippocampus and amygdala), the bilateral pons/medulla brainstem and the bilateral cerebellum; notably, the clusters of hypometabolism were correlated with patient symptoms, including hyposmia and anosmia, memory and cognitive impairment, pain, and insomnia. (Guedj E. et al. 18F-FDG brain PET hypometabolism in patients with long COVID. Eur J Nucl Med Mol Imaging 48, 2823–2833 (2021))
- **At 3 months post-discharge, 55% still complained of neurological symptoms**. (Lu Y, et al. Cerebral micro-structural changes in COVID-19 patients – An MRI-based 3-month follow-up study. EClinicalMedicine. 2020;25:100484).
- At 3 months post-discharge COVID-19 patients' brain structural and metabolic abnormalities correlated with persistent memory loss, anosmia, and fatigue; most patients had only mild COVID-19 at baseline, suggesting that even mild COVID-19 could have persistent effects on the brain. There was statistically significantly higher bilateral gray matter volumes (GMV) which correlated with memory loss and/or loss of smell. These findings indicate possible disruption to micro-structural and functional brain integrity in the recovery stages of COVID-19, suggesting long-term consequences. (Lu Y, et al. Cerebral micro-structural changes in COVID-19 patients – An MRI-based 3-month follow-up study. EClinicalMedicine. 2020;25:100484).
- A PET/CT study found that the most frequent symptoms in non-hospitalised COVID patients 3 months after the infection are headache (68%) and cognitive complaints (81%). (Graham EL, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers" Ann Clin Transl Neurol. 2021;8:1073–1085)
- A systematic review of 84 studies showed that around 88% of COVID patients have abnormal EEG readings (brain electrical activity), particularly in the frontal lobe (33%), where slower electrical discharges were noted. Researchers say this may reveal irreparable brain damage, even after recovering from the virus. These EEG abnormalities correlate with disease severity and pre-existing neurological conditions including epilepsy. In general, the extent of EEG abnormalities correlated with the clinical status of patients and pre-existing neurological diseases. 57% of the follow up EEG studies reported improvement. (Antony AR, Haneef Z. Systematic review of EEG findings in 617 patients diagnosed with COVID-19. Seizure. 2020 Dec;83:234-241)

Neurological conditions: risk factors – no clear consensus

- Patients who had more severe COVID-19 had a higher incidence of these diagnoses at 6 months follow-up. (Taquet M., et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021)
- Cognitive difficulties were not explained by differences in age, education or other demographic and socioeconomic variables. (Hampshire A et al, Cognitive deficits in people who have recovered from COVID-19, EClinicalMedicine, 39, 101044, September 01, 2021)
- A study found that initial COVID-19 severity cannot predict COVID-19-induced encephalopathies, delirium, haemorrhage or stroke (Paterson RW, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020;143(10):3104–3120).
- Delirium in hospitalised patients is a predictor of long-term neurological symptoms and cognitive impairment, especially among older adults. (Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021 Oct;53(10):737-754)
- Immunomodulatory treatments such as corticosteroids used in the acute phase of COVID-19 frequently have CNS adverse effects, including cognitive and sleep disturbances, delirium, psychiatric manifestations, although symptoms resolve after drug withdrawal. (Troyer E.A. et al. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun. 2020;87:34–39)
- A UK study reported that males, older patients and patients with comorbidities were most frequently affected. (Munro KJ, et al. Persistent self-reported changes in hearing and tinnitus in post-hospitalisation COVID-19 cases. Int J Audiol. 2020;59(12):889–890).
- Neurological complications were more common in those who were younger and had severe COVID-19. (Liotta EM et al. (2020). Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. Ann Clin Transl Neurol.7(11):2221–30)

Neurological conditions: Pain

- Long-lasting pain is emerging as a frequent and important complication of SARS-CoV-2, in patients with severe illness but also in non-hospitalised patients with mild- to moderate illness. The pain is often poorly characterised but constitutes an important element of long COVID symptomatology.
- It remains unclear how such pain results from the complex and dynamic interactions of viral-associated long-term organ damage, therapeutic-agent induced side-effects, exacerbation of pre-existing pain, and/or cognitive and psychosocial dysfunction. Similarly, it is unknown if SARS-COV-2 infection exacerbates pre-existing neuropathies (e.g., diabetic neuropathy)
- Such chronic pain often results leads to a decline in quality of life and sedentary life-styles in previously active people.
- The extent of the pain is not associated with severity of the acute disease or biomarker results.

(Korompoki E, et al. Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021 Jul;83(1):1-16)

Neurological conditions: postural orthostatic tachycardia syndrome (POTS)

- POTS is a form of dysautonomia — a disorder of the autonomic nervous system. It manifests as an inappropriate rise in heart rate without change in blood pressure upon movement from a recumbent to an upright position.
- It is essentially a blood circulation disorder characterised by two factors:
  - A specific group of symptoms that frequently occur when standing upright (severe and/or long-lasting fatigue, light-headedness with prolonged sitting or standing that can lead to fainting, brain fog, forceful heartbeats or heart palpitations, nausea and vomiting, headaches, excessive sweating, shakiness, intolerance of exercise or a prolonged worsening of general symptoms after increased activity, pale face and purple discoloration of the hands and feet if the limbs are lower than the level of the heart)
  - A heart rate increase from horizontal to standing (or as tested on a tilt table) of at least 30 beats per minute in adults, or at least 40 beats per minute in adolescents, measured during the first 10 minutes of standing
- POTS is diagnosed only when orthostatic hypotension is ruled out and when there is no acute dehydration or blood loss. Orthostatic hypotension is a form of low blood pressure: 20mm Hg drop in systolic or a 10mm Hg drop in diastolic blood pressure in the first three minutes of standing upright.
- Some Long COVID patients have reported POTS symptoms. Researchers have hypothesised that COVID-19 infection affects the autonomic nervous system, with the cytokine storm resulting from sympathetic activation inducing proinflammatory cytokine release and vagal stimulation resulting in anti-inflammatory responses. Alternatively, COVID-19 related autonomic dysfunction could be mediated by the virus itself and is associated with autoantibodies.

(https://www.hopkinsmedicine.org/health/conditions-and-diseases/postural-orthostatic-tachycardia-syndrome-pots; Aquaro GD, et al., Prognostic value of repeating cardiac magnetic resonance in patients with acute myocarditis, J. Am. Coll. Cardiol. 74 (20) (2019) 2439–2448; Low, R. N., et al. (2020). A Cytokine-based model for the pathophysiology of Long COVID symptoms. https://doi.org/10.31219/osf.io/7gcnv; Dani M, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond). 2021 Jan;21(1):e63-e67)

POTS mechanism and management

- POTS occurs because the body's ways of avoiding a drop in blood pressure when standing up are not working properly. Normally when sitting or standing up, gravity makes some of the blood flow downwards, which can cause a fall in blood pressure by reducing venous return to the heart. The body responds to prevent a fall in blood pressure by narrowing the blood vessels and slightly increasing heart rate.
- But in someone with POTS, these automatic changes don’t occur. When moving to an upright position, the supply of blood to the heart and brain drops, which is detected by baroreceptors in the heart and aorta. They respond by increasing sympathetic neural and adrenergic tone (mediated by noradrenaline and adrenaline respectively). To compensate for lack of stroke volume, this results in tachycardia, experienced as palpitations, breathlessness and chest pain. This is then followed by vasoconstriction in the splanchnic vascular bed, which increases venous return to the heart. (Dani M, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond). 2021 Jan;21(1):e63-e67)
- The BHF says there is no cure for POTS, but it can be managed by diet, exercise and medication. (https://www.bhf.org.uk/informationsupport/heart-matters-magazine/news/coronavirus-and-your-health/long-covid)
- Management of POTS and dysautonomia primarily centres on education, exercise and salt and fluid repletion. Agents such as midodrine can improve vascular tone, while beta-blockers and ivabradine can help manage palpitations (Bryarly M, et al. Postural orthostatic tachycardia syndrome: JACC focus seminar. J Am Coll Cardiol. 2019;73(10):1207–28).

POTS as an autoimmune condition?

- There have been a number of studies suggesting that POTS may have an autoimmune aetiology. A study showed that patients with POTS had a higher prevalence of autoimmune markers and co-morbid autoimmune disorders than the general population. 25% were positive for anti-nuclear antibodies, nearly 33% had some type of autoimmune marker, 20% already had an autoimmune disorder and 11% had Hashimoto's thyroiditis. (Blitshteyn S. Autoimmune markers and autoimmune disorders in patients with postural tachycardia syndrome (POTS). Lupus. 2015 Nov;24(13):1364-9)
- A study showed that most patients with POTS harbour angiotensin II type 1 receptor (AT1R) antibody activity. (Yu X, et al. Angiotensin II Type 1 Receptor Autoantibodies in Postural Tachycardia Syndrome. J Am Heart Assoc. 2018 Apr 4;7(8):e008351)
- In Japanese patients, antiganglionic acetylcholine receptor (gAChR) antibodies were detectable in 29% patients with POTS (Watari M, et al. Autoimmune postural orthostatic tachycardia syndrome. Ann Clin Transl Neurol. 2018 Feb 28;5(4):486-492).
- POTS patients also have elevated autoantibodies to adrenergic receptors (AR) exerting a partial peripheral antagonist effect resulting in a compensatory sympatho-neural activation of α1AR for vasoconstriction and concurrent βAR-mediated tachycardia, facilitated by coexisting β1AR and β2AR agonistic autoantibodies. These findings may explain the increased standing plasma noradrenaline and excessive tachycardia observed in many POTS patients. (Li H, et al. Autoimmune basis for postural tachycardia syndrome. J Am Heart Assoc. 2014 Feb 26;3(1):e000755)

The immune system: predictors of Long COVID

- A study profiled the longitudinal immune response in individuals who had mild COVID **3-4 months after symptom onset**:
- **In patients who did not go on to suffer Long COVID**, acute infection was characterised by **vigorous coordinated innate and adaptive immune activation, with inflammatory cytokine signalling, stronger interferon (IFN) responses** and a potential IFN plasmablast regulatory circuit; in these patients, **the immune and inflammatory response quickly subsided.**
- **In Long COVID patients**, **the acute response was characterised by dampened IFN and antiviral responses coupled with prolonged inflammatory cytokine signalling** in innate immune cells. Other biomarkers suggest ongoing cellular stress and immune cell activation and differentiation.

(Talla, https://www.biorxiv.org/content/10.1101/2021.05.26.442666v3)

Immune impact in Long COVID

- Infectious diseases have long been considered as one of the triggers for autoimmune and autoinflammatory diseases, mainly via molecular mimicry.
- So we will look at:
  - **Autoimmune conditions** in Long COVID: tend to appear during the early, active phase of COVID-19 and persist after the infection has cleared.
  - **Inflammatory conditions** in Long COVID: tend to develop in the weeks after COVID-19.
  - **Lymphopaenia** (abnormally low level of blood lymphocytes, i.e. immune suppression)

(Korompoki E, et al. Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021 Jul;83(1):1-16; Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020 Aug;16(8):413-414)

Autoimmune conditions described with COVID-19

- Guillain-Barre syndrome
- Miller Fisher Syndrome (MFS)
- Antiphospholipid syndrome
- Immune thrombocytopenic purpura
- Evans syndrome
- Systemic lupus erythematosus (SLE)
- Kawasaki disease
- Cold agglutinin disease & autoimmune haemolytic anaemia
- Neuromyelitis optica
- NMDA-receptor encephalitis
- Myasthenia gravis
- Myositis
- Type I diabetes
- Large vessel vasculitis
- Medium vessel vasculitis
- Small vessel vasculitis
- Psoriasis
- Subacute thyroiditis
- Graves' disease
- Sarcoidosis
- Inflammatory arthritis

(Zacharias H, et al. Rheumatological complications of Covid 19. Autoimmun Rev. 2021 Sep;20(9):102883)

Continuing inflammation in Long COVID: a small sample of studies

- A radiological study of Long COVID patients with symptoms persisting for at least 30 days after discharge showed evidence of continuing vascular inflammation (Sollini M, et al. Vasculitis changes in COVID-19 survivors with persistent symptoms: an [(18)F]FDG-PET/CT study. Eur J Nucl Med Mol Imaging. 2020;48(5):1460–1466).
- At 3 months after discharge, levels of proinflammatory cytokines and factors related to vascular injury/repair in Long COVID patients had not returned to normal levels, particularly among those with more serious disease, and cytokine levels correlated with impaired pulmonary function and chest CT abnormalities. (Zhou M, et al. Inflammatory profiles and clinical features of COVID-19 survivors three months after discharge in Wuhan, China. J Infect Dis. 2021;jiab181)
- Blood testing at 1-3 months showed that IL-4 and protein markers of neuronal dysfunction (amyloid beta, neurofilament light, neurogranin, total tau, p-T181-tau) were increased in all COVID-19 participants, while in patients with self-reported neurological problems IL-6 was positively correlated with age or symptom severity and increased SARS-CoV-2 antibodies. This study suggests ongoing peripheral and neuroinflammation after COVID-19 infection. (Sun, B. et al. Characterization and Biomarker Analyses of Post-COVID-19 Complications and Neurological Manifestations. Cells 2021, 10, 386)
- Some studies found no persistent inflammation in Long COVID patients, although this may be due to study differences and the relapsing/remitting nature of Long COVID (Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021 Oct;53(10):737-754).
- In vulnerable individuals, SARS-CoV-2 triggers a dysregulated inflammatory response, known as COVID-19–associated hyperinflammatory syndrome (Webb BJ, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol 2020).

Lymphopaenia

- At around **2 months, 7% of Long COVID patients had persisting lymphopaenia** (Mandal S, et al. Long-COVID': a crosssectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID. Thorax. 2021;76(4):396–398).
- **At 3 months after discharge, lymphopaenia correlated with exertional chest tightness and palpitations** (Liang L, et al. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. J Korean Med Sci. 2020;35(47):e418.)
- Survivors of severe COVID-19 had decreased proportions of T cells, which could correlate with Long COVID. (Lim J, et al. Data-Driven Analysis of COVID-19 Reveals Persistent Immune Abnormalities in Convalescent Severe Individuals. Front Immunol. 2021 Nov 19;12:710217)
- At 4-5 months after diagnosis, a study of paediatric COVID-19 patients found that 42% has lymphopaenia. (Fink TT, et al. Persistent symptoms and decreased health-related quality of life after symptomatic pediatric COVID-19: A prospective study in a Latin American tertiary hospital. Clinics (Sao Paulo). 2021 Nov 26;76:e3511)
- In convalescent patients who had suffered only a mild or asymptomatic infection, followed-up after 3 months, neutrophil dysfunction is responsible for long-term immunosuppression. (Siemińska I. Mild and Asymptomatic COVID-19 Convalescents Present Long-Term Endotype of Immunosuppression Associated With Neutrophil Subsets Possessing Regulatory Functions. Front Immunol. 2021 Sep 29;12:748097)

A closer look at inflammatory conditions potentially implicated in Long COVID

- Multisystem inflammatory syndrome – children (MIS-C)
  aka Paediatric inflammatory multisystem syndrome (PIMS)
- Multisystem inflammatory syndrome – adults (MIS-A)
  aka Severe COVID-19–associated hyperinflammatory syndrome in adults
- Cytokine release syndrome (CIRS)
- Systemic inflammatory response syndrome (SIRS)

Multisystem inflammatory syndrome – children (MIS-C) aka Paediatric inflammatory multisystem syndrome (PIMS)

- This is a **new syndrome seen for the first time with COVID-19; >1,000 cases of MIS-C associated with COVID-19 have now been reported globally.**
- **Children who have had even mild COVID-19 can experience multisystem inflammatory syndrome, with some organs and tissues becoming and remaining severely inflamed.**
- By even July 2020, over 1,000 cases of MIS-C following COVID-19 had been reported globally. MIS-C is a febrile illness, which **could have features of Kawasaki disease**, toxic shock syndrome, acute abdominal conditions, encephalopathy, coronary artery aneurysm and multisystem involvement.
- MIS-C usually occurs 2-4 weeks after COVID-19 infection but it could be as late as 11 weeks later. The prevalence is roughly 2 in 100,000 persons <21 years of age. Most children with MIS-C have antibodies against SARS-CoV-2 and virus may be detected in a smaller proportion.
- **Most children with MIS-C are hospitalised** as they require intense clinical management because of the severity of the disease, which in a few cases is fatal. MIS-C is treatable with drugs such as intravenous immunoglobulin, steroids and other anti-inflammatories to reduce the inflammation and protect the heart, kidneys and other organs from lasting damage.
- A meta-analysis found that children were predominantly male of no particular ethnicity. A higher incidence of gastrointestinal symptoms (84%), myocarditis (62%), left ventricular dysfunction (45%), coronary artery anomaly (17%), pericardial (31%) and neurological symptoms (23%) was reported; 1.6% died.

(https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-long-term-effects/art-20490351; Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. N Engl J Med. 2020 Jul 23;383(4):393-395; Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020 Aug;16(8):413-414; Feldstein LR, et al; Overcoming COVID-19 Investigators; CDC COVID-19 Response Team. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020 Jul 23;383(4):334-346; Dhar. https://doi.org/10.1038/s41390-021-01545-z; Nalbandian A, et al. Post-acute COVID-19 syndrome. Nat Med, 2021; 27, 601–615)

Kawasaki disease

- Kawasaki's disease, aka also known as mucocutaneous lymph node syndrome, is a condition of unknown cause that results in a fever and mainly affects children under 5 years of age and primarily of Asian descent.
- It is a form of vasculitis, where blood vessels become inflamed throughout the body, together with other symptoms.
- The fever typically lasts for more than five days and may not be affected by usual medications
- Although there may be features of Kawasaki's disease, children with MIS-C tend to be older and have a greater range of symptoms, including intestinal involvement, more intense inflammation, toxic shock and greater myocardial injury.

(Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020 Aug;16(8):413-414; Nalbandian A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615; https://www.nhs.uk/conditions/kawasaki-disease/)

MIS-C and MIS-A signs, symptoms and tests

- Ongoing fever PLUS:
  - Stomach pain
  - Bloodshot eyes
  - Vomiting
  - Diarrhoea
  - Weakness, dizziness or lightheadedness (signs of low blood pressure)
  - Skin rash (red spots, blotches or bumps)
  - Acting unusually sleepy or confused
- Laboratory testing may reveal elevated inflammatory markers (CRP, IL-6, fibrinogen, ferritin), coagulopathy (D-dimer) and elevated cardiac markers (troponin).
- Patients with MIS-C and MIS-A are found to be almost universally IgG or IgM antibody positive, but many have negative RT-PCR test results for SARS-CoV-2 infection. This suggests that MIS may result from an aberrant antibody-mediated acquired immune response rather than acute viral infection.
- However, some studies have found them to be positive for other viruses or infections (including Epstein Barr).

(https://www.cdc.gov/mis/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis-c%2Findex.html; Abrams JY, et al. Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. J Pediatr. 2020 Nov;226:45-54.e1; Morris SB, et al. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep. 2020 Oct 9;69(40):1450-1456https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/misc-and-covid19-rare-inflammatory-syndrome-in-kids-and-teens; Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nat Rev Rheumatol. 2020 Aug;16(8):413-414); Nalbandian A, et al. Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615)

MIS-C risk factors

- MIS-C affects mostly school-age children, most commonly 8- and 9-year-olds, but the syndrome also has been seen in infants and young adults.
- It can occur in children who have not had any common symptoms of COVID-19, such as fever, sore throat or cough.
- A French report showed that almost 60% of the children originated from sub-Saharan Africa or the Caribbean and 12% from Asia, while a US study found a relatively high proportion of cases among black, Hispanic, or South Asian children.

(Moreira A. (2020). Kawasaki disease linked to COVID-19 in children. Nature reviews. Immunology, 20(7), 407; Levin M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. N Engl J Med. 2020 Jul 23;383(4):393-395; https://www.cdc.gov/mis/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis-c%2Findex.html; https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/misc-and-covid19-rare-inflammatory-syndrome-in-kids-and-teens)

Cytokine release syndrome (CRS)

- **CRS induces the cytokine storm, mediated by interleukin-6 (IL-6).** (Zhang C, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020 May;55(5):105954)
- IL-6 is known to recruit immune mediators and can drive the cytokine release syndromes (CRS), which can cause local tissue damage and systemic non-protective inflammation. CRS has been detected in SARS-CoV-2-infected patients, and it has been previously known to contribute to the morbidity in patients with SARS-CoV-1 or MERS. (Wang C, et al. The Impact of SARS-CoV-2 on the Human Immune System and Microbiome. Infectious Microbes & Diseases. 2020;3(1):14-21)
- These cytokines recruit immune cells, which then secrete additional cytokines is a **positive feedback loop**; loss of regulation of the inflammatory cascade can result in an uncontrolled destructive process. The cytokine cascade's autoimmune inflammatory effect can be responsible for more damage than is produced directly by the SARS-CoV-2 virus. (Low RN, https://osf.io/7gcnv/)

Systemic inflammatory response syndrome (SIRS)

- Systemic inflammatory response syndrome (SIRS) is an **exaggerated defence response of the body to infection**, trauma, surgery, ischaemia/reperfusion or malignancy. It is an attempt by the body to localise and then eliminate the endogenous or exogenous cause. It involves the release of acute-phase reactants, which are direct mediators of widespread autonomic, endocrine, haematological and immunological alteration in the patient. Even though the purpose is defensive, the **dysregulated cytokine storm can cause a massive inflammatory cascade leading to end-organ dysfunction and even death.** SIRS resulting from a suspected source of infection is termed sepsis. (Chakraborty RK, Burns B. Systemic Inflammatory Response Syndrome. 2021 Jul 28. In: StatPearls; Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 31613449; Hotchkiss RS, et al. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol. 2013 Dec;13(12):862-74)
- SIRS is a **major contributor to COVID-19–associated coagulopathy**, supporting the concept of thromboinflammation. (Masi P, et al. Systemic Inflammatory Response Syndrome Is a Major Contributor to COVID-19-Associated Coagulopathy: Insights From a Prospective, Single-Center Cohort Study. Circulation. 2020 Aug 11;142(6):611-614.)

Compensatory anti-inflammatory response syndrome (CARS)

- SIRS brings with it an **overwhelming and prolonged counterbalancing compensatory anti-inflammatory response syndrome (CARS), principally mediated by transforming growth factor beta (TGF-β).** This leads to postinfectious **immuno-suppression** to dampen the proinflammatory state, prevent maladaptive multiple-organ dysfunction and govern the return to immunologic normalcy. (Oronsky B, et al. A Review of Persistent Post-COVID Syndrome (PPCS). Clin Rev Allergy Immunol. 2021 Feb 20:1–9; Ward NS, et al. The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. Clin Chest Med. 2008;29(4):617-viii)
- **A delicate balance between SIRS and CARS** determines the immediate clinical outcome and, eventually, the prognosis associated with the infection.

Mental health symptoms

- Sleeping disorders,
- Anxiety,
- Post-traumatic stress disorder (PTSD),
- Depression, suicidal ideation/behaviour
- Feeling of isolation from family and friends
- Drug and alcohol abuse,
- Impaired quality of life,
- Distrust of other people,
- Reduced social activity,
- Aggression/irritability,
- Obsessive/compulsive disorder.

References:

Korompoki E, Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021 Jul;83(1):1-16;

Moghimi N, The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 infection. Curr Neurol Neurosci Rep. 2021 Jun 28;21(9):44;

Nalbandian A, Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615;

Bellan M, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open 2021;4:e2036142;

Pavli, A., et al (2021). Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals. Archives of medical research, 52(6), 575–581)

Prevalence of mental health issues

- A study of more than 230,000 mostly American patients shows that **34% of COVID-19 survivors were diagnosed with a neurological or psychiatric disorder within six months**; 12.8% reported that this was their first such diagnosis. An earlier US study found that 20% of COVID-19 survivors were diagnosed with a psychiatric disorder within three months. **Anxiety (17%) and mood disorders (14%) were the most common and were not related to severity of the COVID-19 infection**, although incidence was higher for those who had been hospitalised, and particularly for this who had experienced encephalopathy. Researchers also noted that mental disorders were significantly more common in COVID-19 patients than in comparison groups of people who recovered from flu or other respiratory infections over the same time period. (Taquet M, et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021 May;8(5):416-427)
- Two studies found the **prevalence of PTSD to be around 30% among hospitalised patients** (Nalbandian A, Post-acute COVID-19 syndrome. Nat Med. 2021 Apr;27(4):601-615).
- Anxiety, depression and sleep difficulties were present in approximately 25% of patients at 6 months follow-up (Huang C, 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 16;397(10270):220-232)
- At 1 month after infection, c56% suffered PTSD, depression, anxiety, insomnia and/or obsessive compulsive symptomatology; individual prevalence was PTSD 28%, depression 31%, anxiety 42%, obsessive/compulsive symptoms 20%. (Mazza MG, Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020 Oct;89:594-600)

BUT….

- A 2020 **meta-analysis concluded that the prevalence of anxiety and depression in the background population (with unknown COVID-19 status) during the pandemic was also >30%** (Salari N, Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: a systematic review and meta-analysis. Global Health. 2020 Jul 6;16(1):57)
- **This suggests that the increased incidence of depression/anxiety could be caused by indirect effects of the pandemic.**
- Speaking against this, are several studies in a systematic review where large cohorts of COVID-19 survivors are compared to matched comparison groups (e.g. patients having survived other respiratory diseases during the pandemic), showing that in all but 1 study, COVID-19 survivors were at significantly increased risk of developing depression/anxiety at follow up (Schou TM, et al. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. 2021 Oct;97:328-348).
- Post-traumatic stress disorder: It is important to note that PTSD has been reported continuously throughout the pandemic as an indirect consequence of living under stress, uncertainty and altered daily life rather than due to the disease itself. Also, studies have shown that surviving any critical illness can induce PTSD symptoms. Nonetheless, the reported levels of PTSD are higher than has been found in the background population, where affected individuals are reported to be 7–10%. (Schou TM, et al. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. 2021 Oct;97:328-348)

Psychosocial stressors potentially contributing to Long COVID

- Social isolation,
- Future uncertainty,
- Feelings of helplessness,
- Fear,
- Frustration through lack of support and empathy from family and health care providers,
- Prolonged changes in physical functioning
- Poor healthcare access,
- Racial and gender biases,
- Lack of social support,
- Financial strain
- Separation from loved ones,
- Loss of freedom

(Korompoki E, Epidemiology and organ specific sequelae of post-acute COVID19: A narrative review. J Infect. 2021 Jul;83(1):1-16; Leviner S. Recognizing the Clinical Sequelae of COVID-19 in Adults: COVID-19 Long-Haulers. J Nurse Pract. 2021 Sep;17(8):946-949; Moghimi N, The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 infection. Curr Neurol Neurosci Rep. 2021 Jun 28;21(9):44)

Risk factors for mental health issues

- **A systematic review found that risk factors for mental health issues were disease severity, duration of symptoms, and being female** (Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. 2021 Oct;97:328-348).
- There has been evidence to suggest that persisting psychological symptoms are related to underlying psychiatric or psychological illness (Pavli, A., et al (2021). Post-COVID Syndrome: Incidence, Clinical Spectrum, and Challenges for Primary Healthcare Professionals. Archives of medical research, 52(6), 575–581).
- The admission of patients with severe symptoms to the intensive care unit (ICU) with mechanical ventilation makes them more likely to develop ICU-acquired neuro-cognitive or psychological illnesses such as anxiety, depression and posttraumatic stress disorder (PTSD), although not all studies show this. Two studies showed that depression and anxiety during acute disease and early follow-up time-points were predictors of subsequent development of PTSD. Female sex was generally a risk factor for PTSD, although 1 study found that males were more likely to suffer. (Ramakrishnan RK, et al. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. Front Immunol. 2021 Jun 30;12:686029; Schou TM, et al. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. 2021 Oct;97:328-348)
- Anxiety, depression, distress: children, young adults, healthcare workers, women. (Moghimi N, The Neurological Manifestations of Post-Acute Sequelae of SARS-CoV-2 infection. Curr Neurol Neurosci Rep. 2021 Jun 28;21(9):44)

Duration of mental health issues

- **Generally, anxiety and depressive symptomatology was reported to improve with time** from acute disease (Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. 2021 Oct;97:328-348).
- **Studies are divided over whether PTSD symptoms improve over time** (Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 - A systematic review. Brain Behav Immun. 2021 Oct;97:328-348).

The case against acceptance of mental health issues in Long COVID

- We have seen that particularly for mental health issues, there was an **increased level of depression and anxiety in the population due to lockdown, school closures and other pandemic measures**. Prescriptions of antidepressants to children hit record highs in 2020, while a new CDC report found that emergency hospital attendances for attempted suicide for children aged 12-17 were up by 39% compared to the same period in 2019.
- **If the level was broadly similar, regardless of whether the individual had COVID-19 or not, how can we say that depression and anxiety are actually Long COVID symptoms?** Critics of Long COVID point to this to say that Long COVID is not nearly as prevalent as first thought and can be largely dismissed.
- One article asked if giving such a definitive name – Long Covid – to a mixed bag of symptoms, including symptoms that are actually part and parcel of being a busy working adult, is there a danger that **we have socially constructed a disease**? That we have invented a sickness and, worse, implicitly invited people to identify with this sickness as a way of explaining how they feel. A Lancet article, reported in the Daily Mail suggested that **women with Long COVID may just be menopausal**.
- Early Covid-19 victim Italy has not seen a huge wave of Long Covid cases and nor has the United States been overrun by people who claim to suffer from these long-term symptoms. Apparently, Italy's first-ever Long Covid clinic shut down after just six months. Perhaps Britain is just better at diagnosing Long Covid.
- In the Wall Street Journal, the Canadian psychiatrist Jeremy Devine described Long Covid as "psychosomatic" and "largely an invention of vocal patient activist groups". He believes that the 'hysteria' over Long Covid has convinced many people they have it, when they don't. Others have described Long COVID as "middle-class hypochondria" and questioned whether "the cult of medicalisation is so entrenched that people are now wrapping diagnoses around themselves like comfort blankets, in the belief that a doctor's note is all they need to make sense of their personal failings, fears or sense of exhaustion."

https://www.wsj.com/articles/the-dubious-origins-of-long-covid-11616452583; https://www.spiked-online.com/2021/09/17/is-long-covid-a-myth/; https://www.thetimes.co.uk/article/why-is-britain-now-the-capital-of-long-covid-grjpvzfvw; https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00228-3/fulltext; https://www.dailymail.co.uk/news/article-10160517/Thousands-women-told-long-Covid-just-suffering-menopause-experts-say.html)

The case for acceptance of mental health issues in Long COVID

- Studies showing little difference between Long COVID symptoms and symptom in the background population often **rely on PCR testing, which is unreliable**. Studies that rely on antibody testing may ignore the fact that **antibodies may wane quickly or never develop**. Similarly, some of the depressed population may be asymptomatic or mild COVID-19 sufferers. These may result in **misallocation between cases and controls**.
- These studies and their commentators point to **only a small minority** suffering genuine Long COVID. But even that small minority represents **real people with real suffering** who could be believed and helped. Even if some of the suffering is not due to COVID-19, they are still suffering and can be helped.
- Even if we ignore mental health issues, **what about all the other Long COVID conditions for which there is no increase in prevalence in the population due to pandemic measures**, such as breathlessness, arrhythmia etc.
- We have known for decades that **viruses can cause fatigue and mental health problems** but because this is more common in women, post-viral syndrome has historically been dismissed and overlooked. This is reminiscent of the dismissal of CFS/ME as 'Yuppie Flu' in the 1990s.
- Some have argued that Long COVID cannot exist because there **is no mechanism for it**. What they surely should be saying is that no mechanism has yet been found. But it will, and largely by all the attention being focused on Long COVID. Just because a condition is not understood, it should not be dismissed and ridiculed.
- These sceptics should consider how many conditions (CFS/ME, MCS, autoimmune disease etc) have taken a long time to become recognised, largely because of dismissal not just by doctors but by the commentators of the day.
- Sufferers have had to take matters into their own hands and have formed support and lobbying groups, such as UK groups Long COVID SOS (https://www.longcovidsos.org/) and Long COVID Kids (https://www.longcovidkids.org/) and run their own research projects. This does not tend to happen unless the issue is genuine.

Beware ‘medical gaslighting’

- Medical gaslighting is term used to describe doctors or medical practitioners who blame a patient's illness or symptoms on psychological factors, or deny a patient's illness entirely, for example wrongly telling patients that they are not sick.
- Effectively, these doctors make patients question their own symptoms and sanity.
- Medical gaslighting is now recognised as a form of abuse.
- The term ‘gaslighting’ comes from the Ingrid Bergman film ‘Gaslight’, in which the heroine is manipulated to believe she is losing her mind.