Review Article

Post-COVID-19 Syndrome Mechanisms, Prevention and Management

Abstract

As the population of patients recovering from COVID-19 grows, post COVID-19 challenges are recognizing by ongoing evidences at once. Long COVID is defined as a syndrome with a range of persistent symptoms that remain long after (beyond 12 weeks) the acute SARS-CoV-2 infection. Studies have shown that long COVID can cause multi-organ damages with a wide spectrum of manifestations. Many systems, but not limited to, including respiratory, cardiovascular, nervous, gastrointestinal, and musculoskeletal systems, are involved in long COVID. Fatigue and dyspnea are the most common symptoms of long COVID. Long COVID-19 may be driven by tissue damage caused by virus-specific pathophysiologic changes or secondary to pathological long-lasting inflammatory response because of viral persistence, immune dysregulation, and autoimmune reactions. Some risk factors like sex and age, more than five early symptoms, and specific biomarkers have been revealed as a probable long COVID predicator discussed in this review. It seems that vaccination is the only way for prevention of long COVID and it can also help patients who had already long COVID. Managing long COVID survivors recommended being in a multidisciplinary approach, and a framework for identifying those at high risk for post-acute COVID-19 must be proposed. Possible therapeutic options and useful investigation tools for follow-up are suggested in this review. In sum, as evidence and researches are regularly updated, we provide the current understanding of the epidemiology, clinical manifestation, suspected pathophysiology, associated risk factors, and treatment options of long COVID in this review.

Keywords: *Chronic COVID syndrome, long COVID, long haul COVID, long hauler COVID, post-acute COVID syndrome, post-acute COVID-19 syndrome*

Majed B. Najafi, Shaghayegh H. Javanmard

Applied Physiology Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

Introduction

For the meantime, new challenges of COVID-19 have been emerging. It has been shown that elimination of symptoms and prevention of mortality could not end the COVID-19. So, the main focus on the prevention, diagnosis, and treatment of the hospitalized patients should be switched to a broader perspective. it seems that acute clinical manifestation is just the visible part of the metaphoric COVID-19 iceberg, and post COVID dysfunction, morbidity, and mortality are the submerged part of the iceberg.[1,2] Elisa Perego, a patient from Italy, as a first time, used 'Long-COVID-19′ in May 2020 on social media for describing her lasting symptoms of COVID-19 even after recovery.[3] A citizen's scientist group described Post-COVID syndrome for the first time in spring 2020.[4] it had moved from social media to clinical evaluation of the consequence of COVID patient and persistent symptoms. Long-lasting COVID-19 sequelae and complications such as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia, and decline in quality of life have been mentioned in several papers.[5-7]

Long COVID has been defined as signs and symptoms that last beyond 12 weeks.[8] It can be ongoing symptomatic COVID-19 that persist or relapsing and developing new symptoms and sequel.[9,10] New developed guidelines for managing long COVID like National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) have divided COVID-19 infection into 3 phases – 'Acute COVID-19′ (signs and symptoms of COVID-19 infection up to 4 weeks), 'ongoing symptomatic COVID-19′ (from 4 weeks up to 12 weeks), and 'post-COVID-19 syndrome' (when signs and symptoms continue beyond 12 weeks).[11]

Although the number of people who have recovered from COVID-19 is known, the number of people living with long COVID is unknown. A new meta-analysis on

Address for correspondence:
Dr. Majed B. Najafi, Applied Physiology Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Science, Isfahan, Iran.
E-mail: majedbahri@ymail.com

Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_508_21

Quick Response Code:

How to cite this article: Najafi MB, Javanmard SH. Post-COVID-19 syndrome mechanisms, prevention and management. Int J Prev Med 2023;14:59.

47,910 patients from different counties shows that about 80% (95% CI 65-92) of the infected COVID patients developed at least one or more symptoms.[12]

Recent studies update the collection of symptoms identified in the Long COVID population. More than fifty Long-term effects of COVID-19 have been diagnosed, ranging from most common symptoms, fatigue, headache, attention disorder, hair loss, and dyspnea, to rare neurological and thromboembolic complications that prolonged and involved multisystem and cause significant disability and mortality.[12]

Post-viral syndrome in prior human coronavirus diseases like the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) had been reported lasting up to four years. Similarly, it implies that long COVID can be extended for several months to years.[13,14]

Presently, there is progressively new evidence evolving daily to fulfill the gaps of our limited current knowledge. So living review is needed to update our database. This current review seeks to discuss the epidemiology, organ-specific sequelae, potential pathophysiology, risk factors, and management considerations for long COVID.

Epidemiology

Recent studies evaluate the epidemiology of long COVID for additional problems in diverse follow-up times across different patients in initial disease severity and non or hospitalized setting. Only a meta-analysis in this subject evaluates more than 50 long COVID effects in 47,910 patients between 17 and 87 years old and from 15 to 110 days follow-up time and shows 80% (CI 65–92) patients continue having at least one symptom. Lopez-Leon *et al*.[12] reported fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) were the top common persistent symptoms in long COVID. Carfi *et al*.[5] found that 87.4% of patients had persistence of at least one symptom, particularly fatigue and dyspnea after acute COVID.

Some studies reported the prevalence ranged from 5.2 to 71.8%.[15-20] In these studies, non-hospitalized patients had a lower prevalence (ranging from 5.2 to 36%) than hospitalized (even in ICU) patients that ranged between 39 and 71.8%.[21-23]

The UK's Office for National Statistics (ONS) has reported about 20% (one in five people) have persistent symptoms beyond five weeks, while only 10% (one in ten) have long COVID over 12 weeks.[24] It seems that as times passed after acute COVID, the prevalence of long COVID was declared.

Studies that evaluate long COVID between 3 and 6 months reported the prevalence heterogeneously ranged from 2.3 to 68%.[25,26] The articles that say only highly prevalent hospitalized patients have a higher estimation rate as Venturelli *et al*.[22] reported persistent symptoms in 51% in-hospital discharged patients. On the other side, in studies that included mostly non-hospitalized patients, the prevalence was lower and ranged between 2.3 and 21.4%.[17,19,27]

According to data gathering methods, the prevalence of long COVID was reported differently. By using study app, the prevalence of long COVID after 3 months ranged from 2.3% and 37.7% by using REACT-2.[16,28]

Prevalence also differed if only debilitating symptoms were assessed, using electronic health records estimates ranging from 1.2% of 20-year-old cases to 4.8% of 60-year-old cases after 3 months (CONVALESCENCE).[29]

The prevalence of specific organ damage will be discussed in clinical manifestation.

Pathophysiology

Potential mechanisms contributing to the pathophysiology of Long COVID-19 may be driven by tissue damage caused by virus-specific pathophysiologic changes or secondary to pathological long-lasting inflammatory response because of viral persistence, immune dysregulation, and autoimmune reactions.[30-35]

SARS-CoV-2 enter the cells by angiotensin converting enzyme-2 (ACE2), leading to a disastrous triad of presentation of respiratory insufficiency, acute cardiovascular failure, and coagulopathy.[36] Moreover, hyperinflammatory state, and cytokines storm contribute to multi-organ damage in acute phase.[37]

On the other hand, post-intensive care syndrome which includes new or deteriorating disabilities has been proposed as another mechanism of Long COVID-19 syndrome.[30]

General Sequelea

We discuss the clinical manifestation of long COVID in general and organ-specific parts. General manifestations are more common than organ-specific symptoms. In a meta-analysis the most common manifestation (with prevalence of 25% or greater) were weakness 41%, general malaise 33%, fatigue 31%, concentration impairment 26%, breathlessness 25% and also 37% of people suffer from reduced quality of life (all with 95% CI).[38] It was reported in other analysis that the 5 most common manifestations were fatigue (58%, 95% CI), headache (44%, 95% CI), attention disorder (27% 95% CI), hair loss (25%, 95% CI), dyspnea (24%, 95% CI).[12] Pooled data analysis from other studies showed the 10 most prevalent reported symptoms as (i) fatigue 47% (95% CI); (ii) dyspnea (shortness of breath) 32% (95% CI); (iii) myalgia (muscle pain) 25% (95% CI); (iv) joint pain 20% (95% CI); (v) headache 18% (95% CI); (vi) cough 18% (95% CI); (vii) chest pain 15% (95% CI); (viii) altered smell 14% (95% CI); (ix) altered taste 7% (95%CI); and (x) diarrhea 6% (95% CI).[39] Recent studies of one year follow up assessment in either hospitalized and non-hospitalized patients also revealed that the most common symptoms were fatigue and weakness (52%), muscle and joint pain (48%), sleep disorders (47%), neurological and cognitive impairment (36%), and respiratory disorders (36%).[40] Another symptom reported by patients is sensory alterations which were reported changes in smell in 11% and of taste changes in 7% of discharged patients at a follow-up of 6 months.[7] In another study, about one-third of survivors had sensory alterations, commonly alteration of taste and smell after one year follow up.[41]

There is increasing evidence that COVID-19 will Lead to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). In a study of 1,146 COVID-19 survivors with long COVID, 10.3% had ME/CFS diagnostic.[42] According to a six-month follow-up, 17.5% of COVID-19 survivors still felt fatigued, of whom 14.2% had ME/CFS.[43]

Pulmonary Sequelae

The respiratory system sequel is more than other systems. The most common symptoms are cough and dyspnea, but there are more serious consequences, including post-COVID-19 interstitial lung disease (PC-ILD), lung fibrosis, and DLCO reduction that needs more concern.[3,5,44-46]

There are also other respiratory symptoms, including post-activity polypnea (21.4%), which was caused by just mild activity, chest distress (14.1%), chest pain (12.3%), cough (7.1%), nonmotor polypnea (4.7%), throat pain (3.2%), and excessive sputum (3%) of 538 COVID patients after 3 months follow up.[47] Mixed restrictive and low diffusion patterns were reported in (54%) of patients in a study.[48] The prevalence of dyspnea persistence at 60–100 d follow-up was reported in a range of 42–66%.[49,50] Dyspnea and cough were found in 24% and 19% of patients in a meta-analysis, respectively.[12] Research on 8983 non-hospitalized patients shows that dyspnea and venous thromboembolism are the most important sequels of COVID-19.[51]

The most abnormal findings in chest computed tomography (CT) scan follow-up is the ground glass opacity.[7,52] Varying degrees of radiological abnormalities in the chest CT scans, including consolidation, reticulation, residual ground-glass opacity, interstitial thickening, and fibrotic changes, were reported.[53-55]

Three months after discharge, 71% (39/55) of patients show persistent lung CT scan abnormalities. Thirteen patients (23.64%) showed bilateral involvement, and 15 (27.27%) had evidence of fibrosis (interstitial thickening).[56] Another study revealed that 21% of survivors show fibrosis, with more than 5% affected lung parenchyma.[45]

Some studies showed improvements in radiologic findings over time in serial follow-ups. Tabatabaei *et al*.[57] evaluated chest CT findings of 52 patients at a 3-month follow-up. They reported Thirty (57.7%) patients had complete resolution of radiologic findings, whereas 22 (42.3%) had the residual disease, including ground-glass opacities (54.5%), mixed ground-glass and subpleural parenchymal bands (31.8%), and pure parenchymal bands (13.7%) on follow-up CT. It was shown that persistent radiologic findings correlated with higher CT severity score on the initial exam (P-value 0.036), longer duration of hospitalization, higher rates of ICU admission (all P values <0.05). Outcomes of a US study Among Hospitalized Patients at Sixty-Day follow-up shows that 6.9% of 1250 patients needed supplemental oxygen due to persistent hypoxemia or new requirement for continuous positive airway pressure or other breathing support while sleeping.[49] There is also evidence of impaired 6-min walk test in 24–56% of discharged patients at 6 months follow up with a high correlation with initial COVID phase severity.[7]

DLCO impairment is the commonest lung function test abnormality. Mo *et al*.[58] reported diffusion capacity of the lung for carbon monoxide (DLCO) was abnormal in 47.2% of 110 discharged patients and total lung capacity (TLC) reduction in 25% of them. In other studies, DLCO was reported abnormal in (16.36%) of patients (14/55) at three months after hospital discharge and among 34% (114/334) hospitalized patients at six months of follow-up.[7,56] The DLCO reduction was in a relationship with a high level of D-dimer at admission and with the severity of the illness. D-dimer can be a biomarker predictor for dlco impairment.[56]

Mechanisms of Respiratory System Complications

Damage of the respiratory system could be triggered by both direct viral-dependent mechanisms, including invasion of SARS-CoV-2 to alveolar epithelial and endothelial cells and viral-independent mechanisms secondary to immune cell infiltration.[59]

An interesting study by Sidarta-Oliveira *et al*.,[60] which investigated healthy human lung cell atlas meta-analysis with ~130,000 public single-cell transcriptomes, showed that there are three physiological systems directly involved in the pathogenesis of COVID-19 by ACE2-Receptor: (I) the kinin-kallikrein system; (II) the renin-system angiotensin; (III) and the coagulation system.

Acute alveolar injury is mainly managed by macrophages which phagocyte alveolar debris and produce cytokines and growth factors such as Epidermal growth factor (EGF) and transforming growth factor-alpha (TGF-α). As shown in the COVID-19 autopsy series, the repair process could be followed by fibroproliferative diffuse alveolar damage and microcystic honeycombing seen along in the disease course, similar to other etiologies of ARDS.[61-63]

This fibrosis may be activated by cytokines such as interleukin-6 (IL-6) and transforming growth factor-β, which have been reported pulmonary fibrosis development and may make patients susceptible to bacterial infection.[64]

Autopsy data has indicated single-cell RNA expression patterns same as end-stage pulmonary fibrosis after the resolution of the SARS-CoV-2 infection.[65]

Cardiovascular Sequelae

Common cardiac issues in long COVID are chest pain or tightness, palpitation, exertional dyspnea, dizziness, and an increase in resting heart rate. It has been shown about 12% of COVID-19 patients have persistent acute heart injuries.[7]

Cumulative statistics of Thirty-five studies on 52609 COVID survivors has shown the prevalence of 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 3e6 months follow up. This evidence shows the probability of developing myocardial scarring and fibrosis later, subclinical left and right ventricular dysfunction, and non-ischemic cardiomyopathy.[66]

Studies on athlete populations show lower incidences of myocarditis in athletes. It was a warning that healthy populations such as athletes and asymptomatic/mild COVID survivors could experience myocarditis.[67]

Tachycardia and palpitations are common symptoms reported in 25-50% of patients at 3 months and 9% of survivors after six months.[7] Also High resting heart rate has been reported in 75% of patients who have persistent cardiovascular symptoms (13% of 538 COVID-19 survivors) after 3 months (by (P-value <0.05) with comparison group).[47]

Postural tachycardia syndrome (PoTS) is another post COVID sequel and can be a reason for chest pain, palpitations, and dizziness in long COVID symptoms. There are some case series that show this association.[68,69] Post-COVID -19 tachycardia syndrome is a new term to explain tachycardia in Post-acute COVID-19 that can be presented by pots or inappropriate sinus tachycardia.[70]

In Cardiac Screening Among Professional Athletes, Pericarditis was present in just 0.3% of Prior COVID-19 Infection.[71] In 2 other cardiovascular studies, the Incidence of pericardial effusion was reported 5%.[67,72]

Pooled data of Twenty studies shows cardiac symptoms chest pain (n ¼ 625/4323; median 17.5%), dyspnea (n ¼ 763/4323; median 33%) and palpitations (n ¼ 327/4323; median 0.77%).[66]

The occurrence of arrhythmia was shown 1.7 times higher than matched controls in non-hospitalized survivors at 6-months follow-up.[73] Overall it was shown that COVID survivors have a 3 times higher chance to experience a major adverse cardiac event (heart failure, arrhythmias, and myocardial infarction) at 5 months post-discharge compared to age, sex, and risk factor matched controls.[74]

Mechanisms of Cardiovascular System Complications

Several mechanisms of cardiovascular complications of COVID-19 have been reported, including direct viral invasion, downregulation of ACE2, and inflammation of the myocardium, pericardium, and conduction system. Autopsy studies in 39 cases of COVID-19 showed the presence of virus genome in 62% of patients' heart tissue.[75] The consequent inflammatory response may result in cardiomyocyte death and fibrosis.[76]

Recovered patients may experience increased cardiometabolic demand.[77] This may be associated with decreased cardiac reserve, corticosteroid use and abnormality of the renin-angiotensin-aldosterone system (RAAS). Arrhythmias associated with COVID-19 may be caused by direct cardiac conduction system injury as well as a heightened catecholaminergic state.[78]

Hematologic Sequelae

Thromboembolic events include segmental pulmonary embolism (PE), intracardiac thrombus, thrombosed arteriovenous fistula, ischemic stroke, and hemorrhagic events like subarachnoid hemorrhage are the common hematologic sequel of long COVID.[79-81] There is a limited study, but cumulative statistics on 163 patients without post-discharge thromboprophylaxis show that the thrombosis rate was 2.5% and the hemorrhage rate was 3.7% at day 30 after discharge.[80] Post-discharge venous thromboembolism rate in following 1877 survivors in median 42 d was observed in 4.8 per 1000 discharges.[79] In registry Among 4906 patients (53.7% male, mean age 61.7 y), 90-day post-discharge outcomes show venous thromboembolism (VTE) and arterial thromboembolism (ATE) and all-cause mortality (ACM) rates were 1.55%, 1.71%, and 4.83%, respectively. Also, Post-discharge thromboprophylaxis was prescribed in 13.2%. It was shown that Discharge anticoagulants therapy could make a 46% decrease in major thromboembolism or ACM composite endpoint.[82] Huang *et al*.[7] reported no DVT in 390 participants after 6 months of follow-up.

Mechanisms of Hematologic Complications

COVID-19-associated coagulopathy which is illustrated by high rates (20–30%) of thrombotic rather than bleeding complications in acute COVID-19 is accompanied with a hyperinflammatory and hypercoagulable state.[83] COVID-19-associated thromboinflammation is associated with endothelial dysfunction, complement activation, platelet activation and platelet–leukocyte interactions, and neutrophil extracellular traps, close to the pathophysiology of thrombotic microangiopathy syndromes.[84-88] The chance of thrombotic complications in the post-acute COVID-19 stage is likely connected to the period and severity of a hyperinflammatory state, even though how long the duration is unidentified.

Renal Sequelae

COVID-19 long-haulers—even those who experienced mild cases—are at significantly increased risk for substantial declines in kidney function, such as organ damage and chronic and end-stage kidney disease (ESKD). Surveys on 89,216 survived patients beyond 30 days after their COVID-19 diagnosis has shown a higher risk of AKI (aHR = 1.94), eGFR decline ≥30% (1.25), eGFR decline ≥40% (1.44), eGFR decline ≥50% (1.62), ESKD (2.96), and MAKE (1.66).[89] In other studies, the Incidence of Severe acute kidney injury (AKI) requiring renal replacement therapy (RRT) was reported in 5% of hospitalized survivors and 20–31% of intubated patients.[90-92] There is a close relationship between respiratory failure and AKI, showing that almost 90% of patients getting mechanical ventilation got AKI.[93,94] Fortunately, long-term follow-up revealed High rates of renal recovery in survivors; more than 90% accomplish variable levels of renal restoration, with more than 60% accomplishing total restoration.[95]

Mechanisms of Renal Complications

SARS-CoV-2 has been isolated from renal tissue of COVID-19 patients,[96] and autopsies.[97-100] COVID-19 nephropathy is associated with focal segmental glomerulosclerosis potentially caused by interferon and chemokine activation.[101,102] Thrombi in renal microcirculation may also have a main role in the development of renal injury.[103]

Endocrine Sequelae

Limited Newly diagnosed diabetes mellitus and diabetic ketoacidosis (DKA) has been seen in patients without previous diabetes mellitus weeks to months after acute-COVID.[104-106] Type 2 diabetes mellitus (T2DM) has a bidirectional association with COVID-19. Uncontrolled diabetes can raise the mortality and morbidity incidence of acute COVID and corticosteroid therapy and COVID pandemic have led to the development of diabetes from prediabetes and newly corticosteroid-induced diabetes.[107,108] Another endocrine complication of long COVID is subacute thyroiditis with clinical thyrotoxicosis that has been seen limitedly after acute-COVID.[109,110] Recent case series showed male low serum testosterone (LT) and impaired fertility after 12 weeks follow up.[111]

Mechanisms of Endocrine Complications

Endocrine dysfunction of the post-acute COVID-19 may be induced by direct viral injury, inflammatory damage, and iatrogenic. Antecedent diabetes may turn up through the acute phase of COVID-19.[112] However, there is no existing report of permanent damage to pancreatic β cells.[113] Some studies have shown ACE2 and transmembrane serine protease (TMPRSS2) expression in β cells, which tempting to hypothesize direct viral damage as a cause of insulin deficiency.[114] Moreover, other reasons such as inflammation or the infection stress response and peripheral insulin resistance could be mentioned.[115] To date, it is unclear that COVID-19-associated diabetes how long persist after the acute phase.

Neuropsychiatric Sequelae

Various adverse neurological and psychiatric outcomes under "Neuro-COVID" or "Post-COVID-19 Neurological Syndrome" have been reported. It ranged from mild symptoms like vertigo, "Brain fog," migraine-like headaches, late-onset headaches, alteration in taste and smell sensation (anosmia and ageusia) to complications like seizures, encephalopathy, and stroke.[116-119]

Anosmia and dysgeusia were persisted in approximately 10% of the infected population beyond 2 and 6 months follow-up.[118]

The frequency of ischemic stroke and intracranial hemorrhage rose after COVID-19 to almost one in ten (or three in 100 for a first stroke) patients with encephalopathy.[120,121]

There is evidence that shows an association between COVID-19 and dementia. 6 months evaluation of COVID survivors reveals that 2·66% of patients older than 65 years and 4·72% who had encephalopathy received the first diagnosis of dementia.[122]

Post COVID also affects psychiatric aspects of survivors. Chronic fatigue syndrome, depression, post-traumatic stress disorder (PTSD), substance/drug abuse, and mental health issues such as major mood swings, depression, loneliness and isolation, high levels of stress and anxiety, and sleep-wake disorders have been reported as the long COVID sequel.[123,124]

Brain fog is another common manifestation of LongCOVID-19 and a term used for cognitive impairment of long COVID that is presented by problems in concentration, memory, and dizziness.[42,125] It was shown in a study that cognitive performance might decrease equivalent to a 10-year in the ages between 20 and 70 years.[126]

Several brain regions such as the orbital gyrus, olfactory, gyrus, temporal lobe, amygdala, hippocampus, thalamus, pons/medulla brain stem, and cerebellum were in hypometabolism state in an imaging analysis using positron emission tomography (PET Scan).[127]

Findings Among 62,354 COVID-19 survivors in the USA revealed the overall likelihood of a diagnosis of a new psychiatric illness within 90 d after COVID-19 to be 5.8% (anxiety disorder = 4.7%; mood disorder = 2%; insomnia = 1.9%; dementia.[122]

In a retrospective cohort study of electronic health data from 236379 patients after 6 months follow up the evaluated rate of a neurological or psychiatric diagnosis was 33·62% (95% CI), with 12·84% getting their first such diagnosis. The incidence rate was higher in previously ICU admitted (46·42%). Intracranial hemorrhage frequencies were reported 0·56%, 2·10% for ischemic stroke, 0·11% for parkinsonism, 0·67% for dementia, 17·39% for anxiety disorder, and 1·40% for psychotic illness.[128]

Mechanisms of Neuropsychiatric Complications

Neurologic complications of COVID-19 can be the results of direct viral neuroinflammation or secondary to systemic inflammation, microvascular thrombosis and neurodegeneration.[129-132] Brain autopsies showed that SARS-CoV-2 might cause changes in brain parenchyma and vessels, perhaps due to blood-brain barrier interruption.[133] Acute cerebral injury, characterized by elevated peripheral blood levels of neurofilament light chain, has been found in patients with COVID-19 could be followed by chronic neuronal injury.[134] Since inflammation correlate with cognitive-behavioral changes, persistent neuroinflammation may have a role in neuropsychiatric effects associated with long COVID-19.[135]

Dysfunctional drainage from circumventricular organs has been suggested as another mechanism of neurologic complications of COVID-19.[136]

Post-COVID brain fog in critically ill patients with COVID-19 may arise from mechanisms such as deconditioning or PTSD.[137] Although, COVID-19 brain fog after mild COVID-19 suggest that dysautonomia maybe another underlying mechanism.[138]

Gastrointestinal Sequelae

The Incidence of post-COVID-19 related gastrointestinal symptoms was reported differently in studies but according to the largest cohort until now, GI manifestations were in 18.5% of survivors after 6 months follow up.[139,140] Malnutrition, weight loss, and anorexia are common GI manifestations of long COVID that are not completely resolved after 6 months and need clinical consideration, while GI bleeding, gastroenteritis, and pancreatitis were other complications restored completely after 3 months of acute COVID infection. Malnutrition is the most consistent GI symptom at a half-year follow-up span. A critical piece of patients with these problems might have problems getting weight (i.e., a middle 17.8-pound weight reduction stayed for these patients at a half-year follow-up).[141] Loss of appetite, nausea, acid reflux and diarrhea are other symptoms that persist after 3 months.[142] Viral fecal shedding was seen at least 5 weeks follow up and evidence of viral proliferation and underlying intestinal inflammatory processes like High fecal calprotectin levels were observed.[143,144]

Mechanisms of Gastrointestinal Complications

Some gastrointestinal and hepatobiliary sequelae have been reported in COVID-19 survivors, such as post-infectious irritable bowel syndrome and dyspepsia.[145]

Previous reports have shown that SARS-CoV-2 ribonucleic acid is detectable in the feces of patients even after smear-negative respiratory samples. However, there is no evidence to confirm fecal-oral transmission.[143,146,147]

COVID-19 can change the gut microbiome, potentiate opportunistic infectious organisms and diminish beneficial commensals.[148] The ability of the gut microbiota to alter the course of respiratory infections (gut–lung axis) has been recognized previously in influenza and other respiratory infections.[146,149]

Dermatologic Sequelae

Common dermatologic manifestations of long COVID include skin rash, hair loss, and chilblain-like lesions (pernio). Morbilliform rashes, urticarial eruptions, and papulosquamous lesions are other cutaneous manifestations of COVID that don't persist for a long time.[7,46,150-152]

Just 3% of patients noticed a skin rash at a half-year follow-up in the long COVID-19 Chinese study.[7] The more prevalent dermatologic problem was hair loss, which was presented in around 20% of patients.[46] Post COVID-19 acute telogen effluvium seems to happen at a median of 1.5 months after COVID infection. The majority of our cases were recovered completely after 2 months.[152,153]

Investigation of 538 COVID-19 discharged survivors (54.5% female, middle period of 52.0 years) after 3 months follow-up showed alopecia in 28.6% of the patients.[47]

There are recent studies that showed the persistence of pernio for a long time. It was accepted that Altered microangiopathy of peripheral arterial system supplying hands, foot, and digits are related to chilblain-like lesions (pernio) in Long-COVID-19.[154]

Risk Factors

Patient and clinical characteristics

Although Male sex and older age are risk factors of severe COVID-19, it seems that long COVID is twice more common in women than men.[9,155,156] The UK Office for National Statistics (ONS) also showed that women experience any long COVID symptoms more than men (23.6% versus 20.7%). The prevalence of long COVID was reported in the age group 35-49 years (26.8%), followed by 50-69 years (26.1%), and the ≥70 years group (18%).[157] Analyses of 10 longitudinal research and electronic health records revealed age as an independent risk factor with a linear affiliation with long COVID among age 20-70.[29] In conclusion, female sex may be a risk factor, but further studies are needed.

Most of the studies found no relationship between long COVID and severity of early acute phase disease COVID-19.[119,158-160] However, According to a cross-sectional study, there is a relationship between the severity of acute stages of illness and persistence of manifestation in COVID survivors. It reveals that more severe acute phases can cause the more severe manifestation of long COVID.[106] Similarly, it was shown that patients with more than five symptoms in a cohort study and at least ten symptoms in another study in the acute stages of COVID-19 had an increased risk for developing long COVID.[161,162] Icu admission and prolonged hospitalization are other possible risk factors that were reported in a few studies.[50,163,164]

A Mediterranean cohort study showed no association between baseline clinical features and the development of long COVID-19 syndrome.[21] Analyzed data from 4,182 incident cases of COVID-19 showed that Male sex, age, and preexisting conditions, including obesity, diabetes, and cardiovascular disease, are not predictors of long COVID. Asthma was the only preexisting condition significantly associated with long COVID.[16] Frailty is another risk factor for long COVID even after adjustment with age and comorbidities.[165]

Biomarkers

A Follow-up study of COVID-19 survivors three months after recovery showed Elevated blood urea nitrogen (BUN) and D-dimer levels as risk factors for pulmonary dysfunction in long COVID.[56] Evaluation of Medium-term (2- to 3-month) effects of SARS-CoV-2 infection on post-hospital discharge patients reported a correlation between Systemic inflammatory biomarkers (e.g., CRP, procalcitonin, and neutrophil count) with radiological abnormalities of the heart, liver, and kidney.[164] Increased D-dimer and CRP levels and decreased lymphocytes were found more common in long COVID patients than their fully recovered counterparts.[166] On the other hand, some studies showed no correlation between pro-inflammatory biomarkers (e.g., CRP, D-dimer, IL-6, CD25, and neutrophil and lymphocyte counts) and long COVID syndrome.[21,56,159] Such differences may be due to various study methods like sample characteristics, measured endpoints, and data collection and analyses.

Prevention

Vaccines decrease the chance of long COVID by bringing down the chances of contracting COVID-19 at first. Recent studies on breakthrough cases, vaccinated people who got the coronavirus, suggest that vaccination might have lowering the risk of long COVID. Steves and her colleagues have reported that two-dose vaccination halves the risk of developing long COVID in adults who develop a breakthrough infection. About 11% of the unvaccinated group had symptoms that persisted for at least 28 days, compared to approximately 5% in the vaccinated group of breakthrough infections. Data were recorded from 1.2 million people who received at least one dose of a COVID-19 vaccine from the ZOE COVID App between 8 December 2020 and 4 July 2021.[167,168]

It's also possible that getting vaccinated could reduce long COVID in people who already had long COVID before being vaccinated. In a study published in October 2021, the National Statistical Office used UK coronavirus infection survey data to examine the association between long-term COVID-19 vaccination and long-term COVID-19 in people who had already long COVID before vaccination. They found that the first vaccine was associated with an initial 13% reduction in the likelihood of self-reported long-term COVID. The second dose yielded a further 9% drop relative to the first.[169] A survey conducted by Survivor Corps found that approximately 40% of patients with long-term COVID reported that their symptoms improved after vaccination. However, another 14% said their symptoms have become worse.[170]

Management considerations

Currently, Management options are limited as there is insufficient knowledge of Long-COVID-19. Nevertheless, some clinical guidelines for Managing the long-term effects of COVID-19 to assist clinicians have been proposed.[11,171] It must be a personalized and holistic approach involving monitoring ongoing symptoms and late complications, symptomatic treatment, palliative care, physical rehabilitation, mental health, and psycho-social support.[8,39,172]

The National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), and the Royal College of General Practitioners (RCGP) have released rapid guidelines to assist clinicians.[11,173] These guidelines will be updated in response to new evidence and evolving expert experience.

Physical rehabilitation

Studies up to this point have just suggested that rehabilitation is useful for treating certain cases of long COVID. Light aerobic exercise progressively increases until improvements in fatigue and dyspnea are recommended, typically four to six weeks. Breathing works out that controlling slow, deep breaths will strengthen respiratory muscles and improve exercise capacity, quality of life, and functional outcome.[8,174-176]

A randomized controlled trial (RCT) of 72 elderly long COVID-19 patients has illustrated that a 6-week rehabilitation program (i.e., involving breathing, stretching, and home exercises) restores lung function and enhances exercise capacity, quality of life, and anxiety, but not depression.[177] According to a literature review on rehabilitation of patients post-COVID-19 infection, rehabilitation is contraindicated in post COVID patients with severe pulmonary or cardiac damage. Having a high resting heart rate (>100 beats/min), low or high blood pressure (<90/60 or >140/90 mmHg), and low blood oxygen saturation (<95%) is forbidden for exercise rehabilitation.[178] Similarly, long COVID patients with postural orthostatic tachycardia syndrome (POTS), myalgic encephalomyelitis, or chronic fatigue syndrome (ME/CFS) with post-exertional malaise may not get a positive response from physical rehabilitation.[179-181] A worldwide study showed that 85.9% of members with long COVID experienced the relapse of manifestation after mental or physical activities.[42]

Mental health support

According to Psychological and mental health issues of long COVID, as discussed earlier, mental health support and screening should be done as follow-up care.[8]

Investigation and referral

There is no one-size-fits-all set of surveys and tests due to various symptoms and severity. Still, a full blood count, kidney and liver function, C reactive protein, ferritin, B-type natriuretic peptide, and thyroid function are recommended.[11]

Pulmonary

NICE has suggested that breathlessness should be investigated by an exercise tolerance test suitable for one's abilities, such as the one-minute sit-to-stand test. moreover, guidelines suggested that survivors with persistent respiratory symptoms take a chest x-ray after 12 weeks of infection.[173]

According to NICE guidelines, it may be beneficial to use anti-fibrotic therapy for Patients with pulmonary fibrosis due to COVID19.[182]

Some specialists have proposed assessment with serial PFTs and 6MWTs for people with continual dyspnea, in addition to high-resolution computed tomography of the chest at 6 and 12 months.[183]

According to the British Thoracic Society guideline on long COVID, severe, and mild-to-moderate COVID-19 patients suggested clinical evaluation chest radiography in all patients at 3 months, along with consideration of PFTs, 6MWTs, sputum sampling, and echocardiogram according to clinical assessment. It is also recommended an earlier clinical evaluation for respiratory, psychiatric, and thromboembolic complications after 1-1.5 months discharged in COVID patients who had severe pneumonia, admitted ICU care, old age, or multiple comorbidities.[172]

Cardiovascular

The NICE guidelines on long COVID suggest that Exercise tolerance tests should assess heart function and if there is evidence of postural orthostatic tachycardia syndrome (POTS), for example, palpitations or dizziness on standing, lying, and standing blood pressure, and heart rate recordings should be done (3-minute active stand test, or 10 minutes if you suspect postural tachycardia syndrome).[173]

COVID survivors who had cardiovascular problems during acute COVID phases should be monitored clinically and by electrocardiogram and echocardiogram at 4–12 weeks. It was recommended only for competitive athletes with the COVID cardiovascular sequel to undergo cardiac MRI for 3–6 months until complete resolution.[184,185]

Conclusion

In this review, we have gathered up-to-date data and last published information on the long COVID syndrome. Epidemiology, clinical manifestation, suspected pathophysiology, associated risk factors, and treatment options of long COVID have been reviewed. As time passed, more people recovered from the COVID-19 infection, and the rate of COVID-19 Long Haulers increased, and it has become a great concern and a major health issue worldwide. Growing data and researches improve our knowledge of multi-organ sequelae of COVID-19 and new aspects of this new disease entity. It also helps to promote health policy programs and improvement of patients' management. We lack knowledge about long COVID in any aspect and need further research to be clarified. We need long-term multi-national studies for defining and categorizing persistent symptoms, the pattern of morbidity and mortality, diagnosis criteria, and action plans in managing. The investigation must be between the spectrum of age, gender, race, and concurrent comorbidities. Active and future clinical studies and review of emerging evidence are key to building an informative database for medical practices in this area. Having a 'living' systematic review is necessary for long COVID and evidence should be regularly updated as new researches have been published.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 11 Dec 21 **Accepted:** 24 Dec 21
Published: 24 May 23

References

1. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis 2020;20:773.
2. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S,

Lybeck M, *et al*. A review of persistent post-COVID syndrome (PPCS). Clin Rev Allergy Immunol 2021:1-9. doi: 10.1007/s12016-021-08848-3.

3. Garg M, Maralakunte M, Garg S, Dhooria S, Sehgal I, Bhalla AS, *et al*. The conundrum of 'long-COVID-19': A narrative review. Int J Gen Med 2021;14:2491-506.
4. Carroll E, Neumann H, Aguero-Rosenfeld ME, Lighter J, Czeisler BM, Melmed K, *et al*. Post–COVID-19 inflammatory syndrome manifesting as refractory status epilepticus. Epilepsia 2020;61:e135-e9.
5. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324:603-5.
6. Tenforde MW, Kim SS, Lindsell CJ, Rose EB, Shapiro NI, Files DC, *et al*. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. MMWR Morb Mortal Wkly 2020;69:993-8.
7. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, *et al*. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. Lancet 2021;397:220-32.
8. Greenhalgh T, Knight M, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. BMJ 2020;370:m3026. doi: 10.1136/bmj.m3026.
9. Nabavi N. Long COVID: How to define it and how to manage it. BMJ 2020;370:m3489. doi: 10.1136/bmj.m3489.
10. Garg P, Arora U, Kumar A, Wig N. The "post-COVID" syndrome: How deep is the damage? J Med Virol 2021;93:673-74.
11. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of COVID-19: Summary of NICE, SIGN, and RCGP rapid guideline. BMJ 2021;372:n136. doi: 10.1136/bmj.n136.
12. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, *et al*. More than 50 Long-term effects of COVID-19: A systematic review and meta-analysis. SSRN J 2021. Available from: https://ssrn.com/abstract=3769978.
13. Lee SH, Shin H-S, Park HY, Kim JL, Lee JJ, Lee H, *et al*. Depression as a mediator of chronic fatigue and post-traumatic stress symptoms in Middle East respiratory syndrome survivors. Psychiatry investig 2019;16:59-64.
14. Lam MH-B, Wing Y-K, Yu MW-M, Leung C-M, Ma RC, Kong AP, *et al*. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: Long-term follow-up. Arch Intern Med 2009;169:2142-7.
15. Cellai M, O'Keefe JB, editors. Characterization of prolonged COVID-19 symptoms in an outpatient telemedicine clinic. Open Forum Infectious Diseases: Oxford University Press US; 2020.
16. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, *et al*. Attributes and predictors of long COVID. Nat Med 2021;27:626-31.
17. Cirulli E, Barrett KMS, Riffle S, Bolze A, Neveux I, Dabe S, *et al*. Long-term COVID-19 symptoms in a large unselected population. medrxiv 2020. doi: 10.1101/2020.10.07.20208702.
18. Bliddal S, Banasik K, Pedersen OB, Nissen J, Cantwell L, Schwinn M, *et al*. Acute and persistent symptoms in non-hospitalized PCR-confirmed COVID-19 patients. Sci Rep 2021;11:1-11. doi: 10.1038/s41598-021-92045-x.
19. Havervall S, Rosell A, Phillipson M, Mangsbo SM, Nilsson P, Hober S, *et al*. Symptoms and functional impairment assessed 8 months after mild COVID-19 among health care workers. JAMA 2021;325:2015-6.
20. Nehme M, Braillard O, Alcoba G, Aebischer Perone S, Courvoisier D, Chappuis F, *et al*. COVID-19 symptoms: Longitudinal evolution and persistence in outpatient settings. Ann Intern Med 2021;174:723-5.
21. Moreno-Pérez O, Merino E, Leon-Ramirez J-M, Andres M, Ramos JM, Arenas-Jiménez J, *et al*. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. J Infect 2021;82:378-83.
22. Venturelli S, Benatti SV, Casati M, Binda F, Zuglian G, Imeri G, *et al*. Surviving COVID-19 in Bergamo province: A post-acute outpatient re-evaluation. Epidemiol Infect 2021;149:e32. doi: 10.1017/S0950268821000145.
23. Chiesa-Estomba CM, Lechien JR, Radulesco T, Michel J, Sowerby LJ, Hopkins C, *et al*. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. Eur J Neurol 2020;27:2318-21.
24. Ayoubkhani D. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 April 2021. Off Natl Stat 2021:1-16.
25. Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, *et al*. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA 2021;325:1525-34.
26. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, *et al*. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: Results from a large prospective cohort. Clin Microbiol Infect 2021:1041.e1-1041.e4. doi: 10.1016/j.cmi. 2021.03.012.
27. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, *et al*. Post-COVID syndrome in non-hospitalised patients with COVID-19: A longitudinal prospective cohort study. Lancet Reg Health Eur 2021;6:100122. doi: 10.1016/j.lanepe. 2021.100122.
28. Whitaker M, Elliott J, Chadeau-Hyam M, Riley S, Darzi A, Cooke G, *et al*. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508,707 people. medRxiv 2021. doi: 10.1101/2021.06.28.21259452.
29. Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, *et al*. Risk factors for long COVID: Analyses of 10 longitudinal studies and electronic health records in the UK. medRxiv 2021. doi: 10.1101/2021.06.24.21259277.
30. Inoue S, Hatakeyama J, Kondo Y, Hifumi T, Sakuramoto H, Kawasaki T, *et al*. Post-intensive care syndrome: Its pathophysiology, prevention, and future directions. Acute Med Surg 2019;6:233-46.
31. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, *et al*. COVID-19 and autoimmunity. Autoimmun Rev 2020;19:102597. doi: 10.1016/j.autrev. 2020.102597.
32. Ye G, Pan Z, Pan Y, Deng Q, Chen L, Li J, *et al*. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. J Infect 2020;80:e14-e7.
33. Centers for Diseases Control and Prevention. Investigative criteria for suspected cases of SARS-CoV-2 reinfection (ICR). 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html.
34. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, *et al*. Post-acute COVID-19 syndrome. Nat Med 2021;27:601-15.
35. Stratton CW, Tang YW, Lu H. Pathogenesis-directed therapy of 2019 novel coronavirus disease. J Med Virol 2021;93:1320-42.
36. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, *et al*. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 2020;24:1-10. doi: 10.1186/s13054-020-03120-0.
37. Afrin LB, Weinstock LB, Molderings GJ. COVID-19 hyperinflammation and post-COVID-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis 2020;100:327-32.
38. Michelen M, Cheng V, Manoharan L, Elkheir N, Dagens D,

Hastie C, *et al*. Characterising long term COVID-19: A living systematic review. MedRxiv 2021. doi: 10.1101/2020.12.08.20246025.
39. Aiyegbusi OL, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, *et al*. Symptoms, complications and management of long COVID: A review. J R Soc Med 2021;114:428-42.
40. Lombardo MDM, Foppiani A, Peretti GM, Mangiavini L, Battezzati A, Bertoli S, *et al*. Long-term coronavirus disease 2019 complications in inpatients and outpatients: A one-year follow-up cohort study. Open Forum Infect Dis 2021;8:ofab384. doi: 10.1093/ofid/ofab384.
41. Ngai JC, Ko FW, Ng SS, TO KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology 2010;15:543-50.
42. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, *et al*. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. SSRN J 2021. Available from: https://ssrn.com/abstract=3820561.
43. Simani L, Ramezani M, Darazam IA, Sagharichi M, Aalipour MA, Ghorbani F, *et al*. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. J Neurovirol 2021;27:154-9.
44. Garg M, Prabhakar N, Bhalla AS, Irodi A, Sehgal I, Debi U, *et al*. Computed tomography chest in COVID-19: When & why? Indian J Med Res 2021;153:86-92.
45. Froidure A, Mahsouli A, Liistro G, De Greef J, Belkhir L, Gerard L, *et al*. Integrative respiratory follow-up of severe COVID-19 reveals common functional and lung imaging sequelae. Respir Med 2021;181:106383. doi: 10.1016/j.rmed. 2021.106383.
46. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, *et al*. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. J Infect 2020;81:e4-e6.
47. Xiong Q, Xu M, Li J, Liu Y, Zhang J, Xu Y, *et al*. Clinical sequelae of COVID-19 survivors in Wuhan, China: A single-centre longitudinal study. Clin Microbiol Infect 2021;27:89-95.
48. Frija-Masson J, Debray MP, Gilbert M, Lescure FX, Travert F, Borie R, *et al*. Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post-infection. Eur Respir J 2020;56:2001754. doi: 10.1183/13993003.01754-2020.
49. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. Ann Intern Med 2021;174:576-8.
50. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, *et al*. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol 2021;93:1013-22.
51. Lund LC, Hallas J, Nielsen H, Koch A, Mogensen SH, Brun NC, *et al*. Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: A Danish population-based cohort study. Lancet Infect Dis 2021;21:1373-82.
52. Darcis G, Bouquegneau A, Maes N, Thys M, Henket M, Labye F, *et al*. Long-term clinical follow-up of patients suffering from moderate-to-severe COVID-19 infection: A monocentric prospective observational cohort study. Int J Infect Dis 2021;109:209-16.
53. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, *et al*. Six-month follow-up chest CT findings after severe COVID-19 pneumonia. Radiology 2021;299:E177-86.
54. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, *et al*. Cardiopulmonary recovery after COVID-19: An observational prospective multicentre trial. Eur Respir J 2021;57:2003481. doi: 10.1183/13993003.03481-2020.
55. Alharthy A, Abuhamdah M, Balhamar A, Faqihi F, Nasim N, Ahmad S, *et al*. Residual lung injury in patients recovering from COVID-19 critical illness: A prospective longitudinal point-of-care lung ultrasound study. J Ultrasound Med 2021;40:1823-38.
56. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, *et al*. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 2020;25:100463. doi: 10.1016/j.eclinm. 2020.100463.
57. Tabatabaei SMH, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest CT in COVID-19 pneumonia: What are the findings in mid-term follow-up? Emerg Radiol 2020;27:711-9.
58. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, *et al*. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J 2020;55:2001217. doi: 10.1183/13993003.01217-2020.
59. Huppert LA, Matthay MA, Ware LB, editors. Pathogenesis of acute respiratory distress syndrome. Seminars in Respiratory and Critical Ccare Medicine. Thieme Medical Publishers; 2019.
60. Sidarta-Oliveira D, Jara CP, Ferruzzi AJ, Skaf MS, Velander WH, Araujo EP, *et al*. SARS-CoV-2 receptor is co-expressed with elements of the kinin–kallikrein, renin–angiotensin and coagulation systems in alveolar cells. Sci Rep 2020;10:1-19. doi: 10.1038/s41598-020-76488-2.
61. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, *et al*. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: A two-centre descriptive study. Lancet Infect Dis 2020;20:1135-40.
62. Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, *et al*. Postmortem examination of patients with COVID-19. JAMA 2020;323:2518-20.
63. De Michele S, Sun Y, Yilmaz MM, Katsyv I, Salvatore M, Dzierba AL, *et al*. Forty postmortem examinations in COVID-19 patients: Two distinct pathologic phenotypes and correlation with clinical and radiologic findings. Am J Clin Pathol 2020;154:748-60.
64. Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, *et al*. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020;130:2620-9.
65. Bharat A, Querrey M, Markov NS, Kim S, Kurihara C, Garza-Castillon R, *et al*. Lung transplantation for patients with severe COVID-19. Sci Transl Med 2020;12.
66. Ramadan MS, Bertolino L, Zampino R, Durante-Mangoni E, Monaldi Hospital Cardiovascular Infection Study Group. Cardiac sequelae after coronavirus disease 2019 recovery: A systematic review. Clin Microbiol Infect 2021;27:1250-61.
67. Moulson N, Petek BJ, Drezner JA, Harmon KG, Kliethermes SA, Patel MR, *et al*. SARS-CoV-2 cardiac involvement in young competitive athletes. Circulation 2021;144:256-66.
68. Johansson M, Ståhlberg M, Runold M, Nygren-Bonnier M, Nilsson J, Olshansky B, *et al*. Long-haul post–COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: The Swedish experience. JACC Case Rep 2021;3:573-80.
69. Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn D-I, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. Clin Auton Res 2020;30:449-51.
70. Ståhlberg M, Reistam U, Fedorowski A, Villacorta H, Horiuchi Y, Bax J, *et al*. Post-COVID-19 Tachycardia syndrome:

A distinct phenotype of post-acute COVID-19 syndrome. Am J Med 2021;134:1451-6.
71. Martinez MW, Tucker AM, Bloom OJ, Green G, DiFiori JP, Solomon G, *et al*. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening. JAMA Cardiol 2021;6:745-52.
72. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, *et al*. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J 2021;42:1866-78.
73. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594:259-64.
74. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, *et al*. Post-COVID syndrome in individuals admitted to hospital with COVID-19: Retrospective cohort study. BMJ 2021;372:n693. doi: 10.1136/bmj.n693.
75. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, *et al*. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol 2020;5:1281-5.
76. Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, *et al*. Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020;17:1463-71.
77. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, *et al*. Altered lipid metabolism in recovered SARS patients twelve years after infection. Sci Rep 2017;7:1-12. doi: 10.1038/s41598-017-09536-z.
78. Lazzerini PE, Laghi-Pasini F, Boutjdir M, Capecchi PL. Cardioimmunology of arrhythmias: The role of autoimmune and inflammatory cardiac channelopathies. Nat Rev Immunol 2019;19:63-4.
79. Roberts LN, Whyte MB, Georgiou L, Giron G, Czuprynska J, Rea C, *et al*. Postdischarge venous thromboembolism following hospital admission with COVID-19. Blood 2020;136:1347-50.
80. Patell R, Bogue T, Koshy A, Bindal P, Merrill M, Aird WC, *et al*. Postdischarge thrombosis and hemorrhage in patients with COVID-19. Blood 2020;136:1342-6.
81. Salisbury R, Iotchkova V, Jaafar S, Morton J, Sangha G, Shah A, *et al*. Incidence of symptomatic, image-confirmed venous thromboembolism following hospitalization for COVID-19 with 90-day follow-up. Blood Adv 2020;4:6230-9.
82. Giannis D, Allen SL, Tsang J, Flint S, Pinhasov T, Williams S, *et al*. Postdischarge thromboembolic outcomes and mortality of hospitalized patients with COVID-19: The CORE-19 registry. Blood 2021;137:2838-47.
83. Nicolai L, Leunig A, Brambs S, Kaiser R, Weinberger T, Weigand M, *et al*. Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. Circulation 2020;142:1176-89.
84. Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: The cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020;24:1-8. doi: 10.1186/s13054-020-03062-7.
85. Ghebrehiwet B, Peerschke EI. Complement and coagulation: Key triggers of COVID-19–induced multiorgan pathology. J Clin Invest 2020;130:5674-6.
86. Hottz ED, Azevedo-Quintanilha IG, Palhinha L, Teixeira L, Barreto EA, Pão CR, *et al*. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. Blood 2020;136:1330-41.
87. Szturmowicz M, Demkow U. Neutrophil extracellular traps (NETs) in severe SARS-CoV-2 lung disease. Int J Mol Sci 2021;22:8854. doi: 10.3390/ijms22168854.
88. Song W-C, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest 2020;130:3950-3.
89. Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. J Am Soc Nephrol 2021;32:2851-62.
90. Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J, *et al*. Outcomes for patients with COVID-19 and acute kidney injury: A systematic review and meta-analysis. Kidney Int Rep 2020;5:1149-60.
91. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, *et al*. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: A prospective cohort study. Lancet 2020;395:1763-70.
92. Stevens JS, King KL, Robbins-Juarez SY, Khairallah P, Toma K, Alvarado Verduzco H, *et al*. High rate of renal recovery in survivors of COVID-19 associated acute renal failure requiring renal replacement therapy. PLoS One 2020;15:e0244131. doi: 10.1371/journal.pone. 0244131.
93. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, *et al*. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209-18.
94. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, *et al*. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol 2020;31:1157-65.
95. Stockmann H, Hardenberg J-HB, Aigner A, Hinze C, Gotthardt I, Stier B, *et al*. High rates of long-term renal recovery in survivors of coronavirus disease 2019–associated acute kidney injury requiring kidney replacement therapy. Kidney Int 2021;99:1021-2.
96. Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, *et al*. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98:219-27.
97. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, *et al*. Kidney biopsy findings in patients with COVID-19. J Am Soc Nephrol 2020;31:1959-68.
98. Sharma P, Uppal NN, Wanchoo R, Shah HH, Yang Y, Parikh R, *et al*. COVID-19–associated kidney injury: A case series of kidney biopsy findings. J Am Soc Nephrol 2020;31:1948-58.
99. Golmai P, Larsen CP, DeVita MV, Wahl SJ, Weins A, Rennke HG, *et al*. Histopathologic and ultrastructural findings in postmortem kidney biopsy material in 12 patients with AKI and COVID-19. J Am Soc Nephrol 2020;31:1944-7.
100. Santoriello D, Khairallah P, Bomback AS, Xu K, Kudose S, Batal I, *et al*. Postmortem kidney pathology findings in patients with COVID-19. J Am Soc Nephrol 2020;31:2158-67.
101. Velez JCQ, Caza T, Larsen CP. COVAN is the new HIVAN: The re-emergence of collapsing glomerulopathy with COVID-19. Nat Rev Nephrol 2020;16:565-7.
102. Peleg Y, Kudose S, D'Agati V, Siddall E, Ahmad S, Nickolas T, *et al*. Acute kidney injury due to collapsing glomerulopathy following COVID-19 infection. Kidney Int Rep 2020;5:940-5.
103. Jhaveri KD, Meir LR, Chang BSF, Parikh R, Wanchoo R, Barilla-LaBarca ML, *et al*. Thrombotic microangiopathy in a patient with COVID-19. Kidney Int 2020;98:509-12.
104. Sathish T, Cao Y, Kapoor N. Newly diagnosed diabetes in COVID-19 patients. Prim Care Diabetes 2020;15:194.
105. Akter F, Mannan A, Mehedi HH, Rob MA, Ahmed S, Salauddin A, *et al*. Clinical characteristics and short term outcomes after recovery from COVID-19 in patients with

and without diabetes in Bangladesh. Diabetes Metab Syndr 2020;14:2031-8.
106. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract 2021;75:e13746. doi: 10.1111/ijcp. 13746.
107. Ghosh A, Anjana RM, Rani CSS, Rani SJ, Gupta R, Jha A, *et al*. Glycemic parameters in patients with new-onset diabetes during COVID-19 pandemic are more severe than in patients with new-onset diabetes before the pandemic: NOD COVID India Study. Diabetes Metab Syndr 2021;15:215-20.
108. Yuan K, Gong Y-M, Liu L, Sun Y-K, Tian S-S, Wang Y-J, *et al*. Prevalence of posttraumatic stress disorder after infectious disease pandemics in the twenty-first century, including COVID-19: A meta-analysis and systematic review. Mol Psychiatry 2021;26:4982-4998.
109. Ruggeri RM, Campennì A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-COV-2: An endocrine complication linked to the COVID-19 pandemic. Hormones 2021;20:219-21.
110. Brancatella A, Ricci D, Viola N, Sgrò D, Santini F, Latrofa F. Subacute thyroiditis after Sars-COV-2 infection. J Clin Endocrinol Metab 2020;105:2367-70.
111. Moreno-Perez O, Merino E, Alfayate R, Torregrosa ME, Andres M, Leon-Ramirez JM, *et al*. Male pituitary-gonadal axis dysfunction in post-acute COVID-19 syndrome. Prevalence and associated factors: A Mediterranean case series. Clin Endocrinol 2021. doi: 10.1111/cen. 14537.
112. Mondal S, DasGupta R, Lodh M, Gorai R, Choudhury B, Hazra AK, *et al*. Predictors of new-onset diabetic ketoacidosis in patients with moderate to severe COVID-19 receiving parenteral glucocorticoids: A prospective single-centre study among Indian type 2 diabetes patients. Diabetes Metab Syndr 2021;15:795-801.
113. Gentile S, Strollo F, Mambro A, Ceriello A. COVID-19, ketoacidosis and new-onset diabetes: Are there possible cause and effect relationships among them? Diabetes Obes Metab 2020;22:2507-8.
114. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47:193-9.
115. Farag AA, Hassanin HM, Soliman HH, Sallam A, Sediq AM, Elbanna K. Newly diagnosed diabetes in patients with COVID-19: Different types and short-term outcomes. Trop Med Infect Dis 2021;6:142. doi: 10.3390/tropicalmed6030142.
116. Baig AM. Deleterious outcomes in long-hauler COVID-19: The effects of SARS-CoV-2 on the CNS in chronic COVID syndrome. ACS Chem Neurosci 2020;11:4017-20.
117. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. J Neurol Sci 2020;419. doi: 10.1016/j.jns. 2020.117179
118. Boscolo-Rizzo P, Borsetto D, Fabbris C, Spinato G, Frezza D, Menegaldo A, *et al*. Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. JAMA Otolaryngol Head Neck Surg 2020;146:729-32.
119. Lu Y, Li X, Geng D, Mei N, Wu P-Y, Huang C-C, *et al*. Cerebral micro-structural changes in COVID-19 patients–an MRI-based 3-month follow-up study. EClinicalMedicine 2020;25:100484.
120. Siow I, Lee KS, Zhang JJ, Saffari SE, Ng A, Young B. Stroke as a neurological complication of COVID-19: A systematic review and meta-analysis of incidence, outcomes and predictors. J Stroke Cerebrovasc Dis 2021;30:105549. doi: 10.1016/j. jstrokecerebrovasdis. 2020.105549.
121. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, Collado-Jiménez R, Ayo-Martín Ó, Barrena C, *et al*. Cerebrovascular disease in patients with COVID-19: Neuroimaging, histological and clinical description. Brain 2020;143:3089-103.
122. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry 2021;8:130-40.
123. Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. JAMA 2020;324:1723-4.
124. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, *et al*. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun 2020;89:594-600.
125. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: A review. JAMA Neurol 2020;77:1018-27.
126. Mendelson M, Nel J, Blumberg L, Madhi S, Dryden M, Stevens W, *et al*. Long-COVID: An evolving problem with an extensive impact. S Afr Med J 2021;111:10-2.
127. Guedj E, Campion J, Dudouet P, Kaphan E, Bregeon F, Tissot-Dupont H, *et al*. 18 F-FDG brain PET hypometabolism in patients with long COVID. Eur J Nucl Med Mol Imaging 2021;48:2823-33.
128. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: A retrospective cohort study using electronic health records. Lancet Psychiatry 2021;8:416-27.
129. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alzheimer’s Res Ther 2020;12:1-3. doi: 10.1186/s13195-020-00640-3.
130. Muccioli L, Pensato U, Cani I, Guarino M, Cortelli P, Bisulli F. COVID-19-associated encephalopathy and cytokine-mediated neuroinflammation. Ann Neurol 2020;88:860-1.
131. Pilotto A, Padovani A. Reply to the letter” COVID-19-associated encephalopathy and cytokine-mediated neuroinflammation”. Ann Neurol 2020;88:861-2.
132. South K, McCulloch L, McColl BW, Elkind MS, Allan SM, Smith CJ. Preceding infection and risk of stroke: An old concept revived by the COVID-19 pandemic. Int J Stroke 2020;15:722-32.
133. Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of COVID-19: A spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. Acta Neuropathol 2020;140:1-6.
134. Ameres M, Brandstetter S, Toncheva AA, Kabesch M, Leppert D, Kuhle J, *et al*. Association of neuronal injury blood marker neurofilament light chain with mild-to-moderate COVID-19. J Neurol 2020;267:3476-8.
135. Bortolato B, F Carvalho A, K Soczynska J, I Perini G, S McIntyre R. The involvement of TNF-α in cognitive dysfunction associated with major depressive disorder: An opportunity for domain specific treatments. Curr Neuropharmacol 2015;13:558-76.
136. Perrin R, Riste L, Hann M, Walther A, Mukherjee A, Heald A. Into the looking glass: Post-viral syndrome post COVID-19. Med Hypotheses 2020;144:110055. doi: 10.1016/j.mehy. 2020.110055.
137. Kaseda ET, Levine AJ. Post-traumatic stress disorder: A differential diagnostic consideration for COVID-19 survivors. Clin Neuropsychol 2020;34:1498-514.
138. Miglis MG, Goodman BP, Chemali KR, Stiles L. Re:

'Post-COVID-19 chronic symptoms' by Davido *et al*. Clin Microbiol Infect 2021;27:494.
139. Tian Y, Rong L, Nian W, He Y. gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther 2020;51:843-51.
140. Schmulson M, Dávalos M, Berumen J. Beware: Gastrointestinal symptoms can be a manifestation of COVID-19. Rev Gastroenterol Méx (Engl Ed) 2020;85:282-7.
141. Rizvi A, Patel Z, Liu Y, Satapathy SK, Sultan K, Trindade AJ, *et al*. Gastrointestinal sequelae 3 and 6 months after hospitalization for coronavirus disease 2019. Clin Gastroenterol Hepatol 2021;271-81.
142. Weng J, Li Y, Li J, Shen L, Zhu L, Liang Y, *et al*. Gastrointestinal sequelae 90 days after discharge for COVID-19. Lancet Gastroenterol Hepatol 2021;6:344-6.
143. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, *et al*. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol 2020;5:434-5.
144. Effenberger M, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, *et al*. Faecal calprotectin indicates intestinal inflammation in COVID-19. Gut 2020;69:1543-4.
145. Wang MK, Yue HY, Cai J, Zhai YJ, Peng JH, Hui JF, *et al*. COVID-19 and the digestive system: A comprehensive review. World J Clin Cases 2021;9:3796-813.
146. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, *et al*. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. Gastroenterology 2020;159:81-95.
147. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020;158:1831-3.e3.
148. Donati Zeppa S, Agostini D, Piccoli G, Stocchi V, Sestili P. Gut microbiota status in COVID-19: An unrecognized player? Front Cell Infect Microbiol 2020;10:576551. doi: 10.3389/fcimb. 2020.576551.
149. Bradley KC, Finsterbusch K, Schnepf D, Crotta S, Llorian M, Davidson S, *et al*. Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. Cell Rep 2019;28:245-56 e4.
150. McMahon DE, Gallman AE, Hruza GJ, Rosenbach M, Lipoff JB, Desai SR, *et al*. Long COVID in the skin: A registry analysis of COVID-19 dermatological duration. Lancet Infect Dis 2021;21:313-4.
151. Tammaro A, Parisella FR, Adebanjo GAR. Cutaneous long COVID. J Cosmet Dermatol 2021;20:2378-9.
152. Moreno-Arrones O, Lobato-Berezo A, Gomez-Zubiaur A, Arias-Santiago S, Saceda-Corralo D, Bernardez-Guerra C, *et al*. SARS-CoV-2-induced telogen effluvium: A multicentric study. J Eur Acad Dermatol Venereol 2021;35:e181-3.
153. Abrantes TF, Artounian KA, Falsey R, Simão JCL, Vañó-Galván S, Ferreira SB, *et al*. Time of onset and duration of post-COVID-19 acute telogen effluvium. J Am Acad Dermatol 2021;85:975-6.
154. Mehta P, Bunker CB, Ciurtin C, Porter JC, Chambers RC, Papdopoulou C, *et al*. Chilblain-like acral lesions in long COVID-19: Management and implications for understanding microangiopathy. Lancet Infect Dis 2021;21:912. doi: 10.1016/ S1473-3099(21)00133-X.
155. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, Crooks MG. Post-COVID-19 symptom burden: What is long-COVID and how should we manage it? Lung 2021;199:113-9.
156. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, *et al*. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. Plos One 2020;15:e0240784.
157. Office for National Statistics. UK Office for National Statistics. Prevalence of long COVID symptoms and COVID-19 complications. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/datasets/prevalenceoflongCOVIDsymptomsandCOVID19complications.
158. Miyazato Y, Morioka S, Tsuzuki S, Akashi M, Osanai Y, Tanaka K, *et al*., editors. Prolonged and late-onset symptoms of coronavirus disease 2019. Open Forum Infectious Diseases. Oxford University Press US; 2020.
159. van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, *et al*. Comprehensive health assessment 3 months after recovery from acute coronavirus disease 2019 (COVID-19). Clin Infect Dis 2021;73:e1089-98.
160. Poyraz BÇ, Poyraz CA, Olgun Y, Gürel Ö, Alkan S, Özdemir YE, *et al*. Psychiatric morbidity and protracted symptoms after COVID-19. Psychiatry Res 2021;295:113604. doi: 10.1016/j.psychres. 2020.113604.
161. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, *et al*. Attributes and predictors of Long-COVID: Analysis of COVID cases and their symptoms collected by the COVID symptoms study app. medRxiv 2020. doi: 10.1101/2020.10.19.20214494.
162. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Persistent symptoms 1.5–6 months after COVID-19 in non-hospitalised subjects: A population-based cohort study. Thorax 2021;76:405-7.
163. Taboada M, Cariñena A, Moreno E, Rodríguez N, Domínguez MJ, Casal A, *et al*. Post-COVID-19 functional status six-months after hospitalization. J Infect 2021;82:e31-3.
164. Raman B, Cassar MP, Tunnicliffe EM, Filippini N, Griffanti L, Alfaro-Almagro F, *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;31:100683. doi: 10.1016/j.eclinm. 2020.100683.
165. Hewitt J, Carter B, Vilches-Moraga A, Quinn T, Braude P, Verduri A. Th e effect of frailty on survival in patients with COVID-19 (COPE): A multicentre, European, observational cohort study. Lancet Public Health 2020;5:e444-51.
166. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, Hare SS, *et al*. 'Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021;76:396-8.
167. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, *et al*. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: A prospective, community-based, nested, case-control study. Lancet Infect Dis 2021;22:43-55.
168. Ledford H. Do vaccines protect against long COVID? What the data say. Nature 2021;599:546-8.
169. Office for National Statistics. Coronavirus (COVID-19) vaccination and self-reported long COVID in the UK: 25 October 2021. 2021. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronavirus COVID19vaccinationandselfreportedlongCOVIDintheuk/25october2021.
170. Akrami A, Assaf G, Davis H, Harris K, Iwasaki A, Krumholz H, *et al*. Change in symptoms and immune response in people with post-acute sequelae of SARS-Cov-2 infection (PASC) after SARS-Cov-2 vaccination. medRxiv 2021. doi: 10.1101/2021.07.21.21260391.

171. Guideline N. NICE Guideline; COVID-19 rapid guideline: Managing the long-term effects of COVID-19. Available from: https://www.nice.org.uk/guidance/ng188.
172. George PM, Barratt SL, Condliffe R, Desai SR, Devaraj A, Forrest I, *et al*. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax 2020;75:1009-16.
173. Sivan M, Taylor S. NICE guideline on long COVID. BMJ 2020;371:m4938. doi: 10.1136/bmj.m4938.
174. Barker-Davies RM, O'Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, *et al*. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med 2020;54:949-59.
175. Wang TJ, Chau B, Lui M, Lam G-T, Lin N, Humbert S. PM&R and pulmonary rehabilitation for COVID-19. Am J Phys Med Rehabil 2020. doi: 10.1097/PHM.0000000000001505.
176. Grigoletto I, Cavalheri V, de Lima FF, Ramos EMC. Recovery after COVID-19: The potential role of pulmonary rehabilitation. Braz J Phys Ther 2020;24:463-4.
177. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract 2020;39:101166. doi: 10.1016/j.ctcp. 2020.101166.
178. Demeco A, Marotta N, Barletta M, Pino I, Marinaro C, Petraroli A, *et al*. Rehabilitation of patients post-COVID-19 infection: A literature review. J Int Med Res 2020;48:0300060520948382. doi: 10.1177/0300060520948382.
179. Fu Q, Levine BD. Exercise and non-pharmacological treatment of POTS. Auton Neurosci 2018;215:20-7.
180. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev 2019;10:CD003200. doi: 10.1002/14651858.CD003200.pub8.
181. Twisk F, Maes M. A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. Neuro Endocrinol Lett 2009;30:284-99.
182. Torrisi SE, Kahn N, Vancheri C, Kreuter M. Evolution and treatment of idiopathic pulmonary fibrosis. Presse Méd 2020;49:104025. doi: 10.1016/j.lpm. 2020.104025.
183. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: Monitoring the clinical course in survivors. Lancet Respir Med 2020;8:839-42.
184. Desai AD, Boursiquot BC, Melki L, Wan EY. Management of arrhythmias associated with COVID-19. Curr Cardiol Rep 2021;23:1-9. doi: 10.1007/s11886-020-01434-7.
185. Hendren NS, Drazner MH, Bozkurt B, Cooper Jr LT. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation 2020;141:1903-14.