Review Article

Post-COVID-19 Syndrome Mechanisms, Prevention and Management

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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*

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

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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. Carfì *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.

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