Review

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A multidisciplinary review of long COVID to address the challenges in diagnosis and updated management guidelines

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Abstract

Long COVID has emerged as a significant challenge since the COVID-19 pandemic, which was declared as an outbreak in March 2020, marked by diverse symptoms and prolonged duration of disease. Defined by the WHO as symptoms persisting or emerging for at least two months post-SARS-CoV-2 infection without an alternative cause, its prevalence varies globally, with estimates of 10–20% in Europe, 7.3% in the USA, and 3.0% in the UK. The condition's etiology remains unclear, involving factors, such as renin–angiotensin system overactivation, persistent viral reservoirs, immune dysregulation, and autoantibodies. Reactivated viruses, like EBV and HSV-6, alongside epigenetic alterations, exacerbate mitochondrial dysfunction and energy imbalance. Emerging evidence links SARS-CoV-2 to chromatin and gut microbiome changes, further influencing long-term health impacts. Diagnosis of long COVID requires detailed systemic evaluation through medical history and physical examination. Management is highly individualized, focusing mainly on the patient's symptoms and affected systems. A multidisciplinary approach is essential, integrating diverse perspectives to address systemic manifestations, underlying mechanisms, and therapeutic strategies. Enhanced understanding of long COVID's pathophysiology and clinical features is critical to improving patient outcomes and quality of life. With a growing number of cases expected globally, advancing research and disseminating knowledge on long COVID remain vital for developing effective diagnostic and management frameworks, ultimately supporting better care for affected individuals.

Keywords: epidemiology, epigenetics, long COVID, management, systemic manifestations

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HIGHLIGHTS

- Long COVID affects multiple organ systems, with symptoms ranging from fatigue and respiratory issues to neurological and cardiovascular complications, significantly impacting quality of life.
- Immune dysregulation, viral persistence, autoantibodies, and epigenetic changes are among the key mechanisms hypothesized to drive the prolonged symptoms of long COVID.
- Epidemiological studies reveal notable risk factors for long COVID, including gender, age, pre-existing conditions, and the severity of the acute infection, while highlighting its prevalence in various populations.
- Diagnosis of long COVID remains challenging due to the variability of symptoms, necessitating the use of biomarkers, imaging, and functional assessments for comprehensive evaluation.
- Multidisciplinary approaches to management, including symptom-based therapies, rehabilitation programs, and targeted clinical care, are crucial for improving outcomes for individuals with long COVID.

Background

On 11 March 2020, WHO considered the COVID-19 outbreak as a worldwide pandemic. This illness is brought on by SARS-CoV-2, a coronavirus that causes severe acute respiratory syndrome, which, since then, has been a controversial topic between scientists with its presentations, morbidities, and duration[1]. When an individual first caught the virus, he enters an acute phase of the disease, which is generally defined as the first 5 weeks of infection[2]. However, several authorities have formulated a definition for the long-lasting disease. The National Institute for Health and Care Excellence (NICE) has reported it in its guideline as a long-standing symptoms, whether they are physical, cognitive, and/or psychological, that lasts for more than 12 weeks after the initial illness and with the absence of any alternative diagnosis for these symptoms[3]. WHO has also added that symptoms should last for more than 2 months. The Association of the Scientific Medical Societies in Germany considered the functional status and new emerging symptoms after the acute phase as criteria for long COVID recognition[4].

Symptoms of long COVID have some of the main characteristics of acute-phase disease. It may involve multiple organs. The most often mentioned symptoms of long COVID include: dyspnea, fatigue, hair loss, and attention disorder[5]. In addition to lung causality, the central nervous, cardiovascular, and musculoskeletal systems may also be involved. Psychological consequences are also of clinical significance[4]. It should be noted that symptoms fluctuate widely in intensity and coincide with other COVID-19-related illnesses, like post-intensive care syndrome or the deterioration of pre-existing medical disorders, making a challenge to recognize symptoms[6].

Several clinical approaches are used to confirm suspected long COVID disease. Studies have showed the role of high interleukin (IL)-17 and IL-2 and low IL-10, IL-6, and IL- 4 levels in long COVID diagnosis. Other studies have linked certain biomarkers with specific system casualties. Imaging studies are enrolled in suspected long COVID conditions, showing little progress in chest radiographs, and more notable changes on CT scans. Functional tests used for patients follow up include pulmonary tests, cardiovascular tests, and exercise intolerance[7]. Due to the high heterogeneity in symptoms, making decisions regarding its management requires regular monitoring of long COVID patients. The most commonly followed management approach is symptom-based therapy. A detailed medical history and physical examination are crucial. Referrals to the concerned specialists are also required for potent clinical care[2].

Our objective in this study is to give a comprehensive review of long COVID assessing the systemic signs and symptoms, underlying causes, and available treatments for the condition. We also wanted to give a special highlight to the epigenetics involved in the pathogenesis of the disease illness. Furthermore, our study also explores the role of viruses, like EBV and HSV-6, immunological dysregulation, autoantibodies, epigenetic modifications, and changes in the gut microbiome as potential contributors to persistent symptoms. By taking a multidisciplinary approach, this review aims to provide a better understanding of long COVID, leading to improved clinical care, prognosis, and general well-being for those affected by this potentially new chronic disease. As long COVID cases are expected to increase in the future, such knowledge is crucial for effective management and treatment.

Epidemiology of long COVID

More than 17 million people in the European region were affected by long COVID over the first 2 years of the pandemic, according to WHO records, with around 10–20% estimated prevalence[8].

In a survey study representing the US population, investigators assessed 3042 US adults aged 18 and above to estimate long COVID prevalence. They used a questionnaire developed by UK's Office of National Statistics. Long COVID has been determined by relying on individuals' responds to the self-questionnaire. People without a history of COVID-19 infection or those who had symptoms that persisted for less than a month were not included in the study. Results showed an estimated prevalence of 7.3% (95% confidence interval, CI: 6.1–8.5%), with 18.5 million adults living in the US. After considering age and gender factors, females have higher prevalence of long COVID (aPR: 1.84) compared with males. Individuals aging 65 years or older have lower prevalence of long COVID. Higher prevalence have been observed between white individuals compared to other ethnicities[9].

The former study results were consistent with HPS US (Household Pulse Survey), which consists of added questions by National Center for Health Statistics (NCHS) to evaluate long COVID prevalence among US adult citizens. The estimates in this survey showed a prevalence of 7.5%[10].

Considering the same period, the office of national statistics in the UK revealed the occurrence of self-reported long COVID using a national survey data. The results showed that around 2.0 million people (3.0%) in the UK living in private households have experienced persistent symptoms of a COVID-19 infection longer than 4 weeks[11]. On its latest update as of 5 March 2023, the estimates were about 1.9 million people (2.9%) suffering from long COVID[11].

It is important to note that UK data involves a population aged two years and older. Children's and adolescents' prevalence have significant differences compared to adults. Studies show prevalence percentage of long COVID ranging from 1.6% to 70% for this population. A case–control study in France showed only 1% affected children with long COVID, while a cohort study in Latvia had a prevalence of 70%. Italian studies also resulted in different estimates. 56.7% was the result of a cross-sectional Italian study used ISARIC questionnaire. Another study has questioned pediatricians about long-lasting symptoms of COVID-19 and revealed a prevalence of 20%. The CLoCK study is a cohort matched study assessed long COVID prevalence among a different number of symptoms. Results of long COVID with one persistent symptom was 66.5%, while it was 30.3% with three persistent symptoms. Importantly noted that the difference between case and control groups, 53.4% and 16.2%, respectively, was higher with an increased number of symptoms[12].

A national cohort study has been conducted on 37 522 children aged 0–17 years among the Danish population to assess long COVID between children. 15 041 children with positive SARS-CoV-2 results were considered included in the case group- and 15 080 children in the control group. 12–51% of case group children experienced symptoms for more than 4 weeks. The percent increased with age. In the control group, 15–38% of children have symptoms >4 weeks and the percent also increased with age[13]. Another national, cross-sectional study (LongCOVIDKidsDK) in Denmark investigated long COVID symptoms of adolescents aged 15–18 years matched with

a control group. 6630 adolescents participated in the case group and 21 640 were in the control group. Results showed a higher odds ratio between the case group of reporting persistent COVID-19 symptoms[14].

The pathophysiology of multi-organ involvement and mechanisms of tissue impairment in long COVID

Researchers have put several presumptions regarding long COVID pathophysiology, especially as this disease has multi-organ involvement.

One of the suggested theories of long COVID pathophysiology is the effect of overactivation of the renin-angiotensin system (RAS) (Fig. 1). SARS-CoV-2 attaches to ACE2 receptors with its protein spikes, which triggers a sequence of processes and leads to over-activation of AT1R. ACE2 receptors are scattered in different vital organs, making this mechanism an important possible cause of multi-system impairment correlated to long COVID. The resulted outcomes may be tissue fibrosis in heart, lungs, kidneys, and liver; inflammation; vasoconstriction; and hypertension[15].

Currently, the effects of immune response on long COVID are beiong investigated. Several hypotheses have been assessed, which

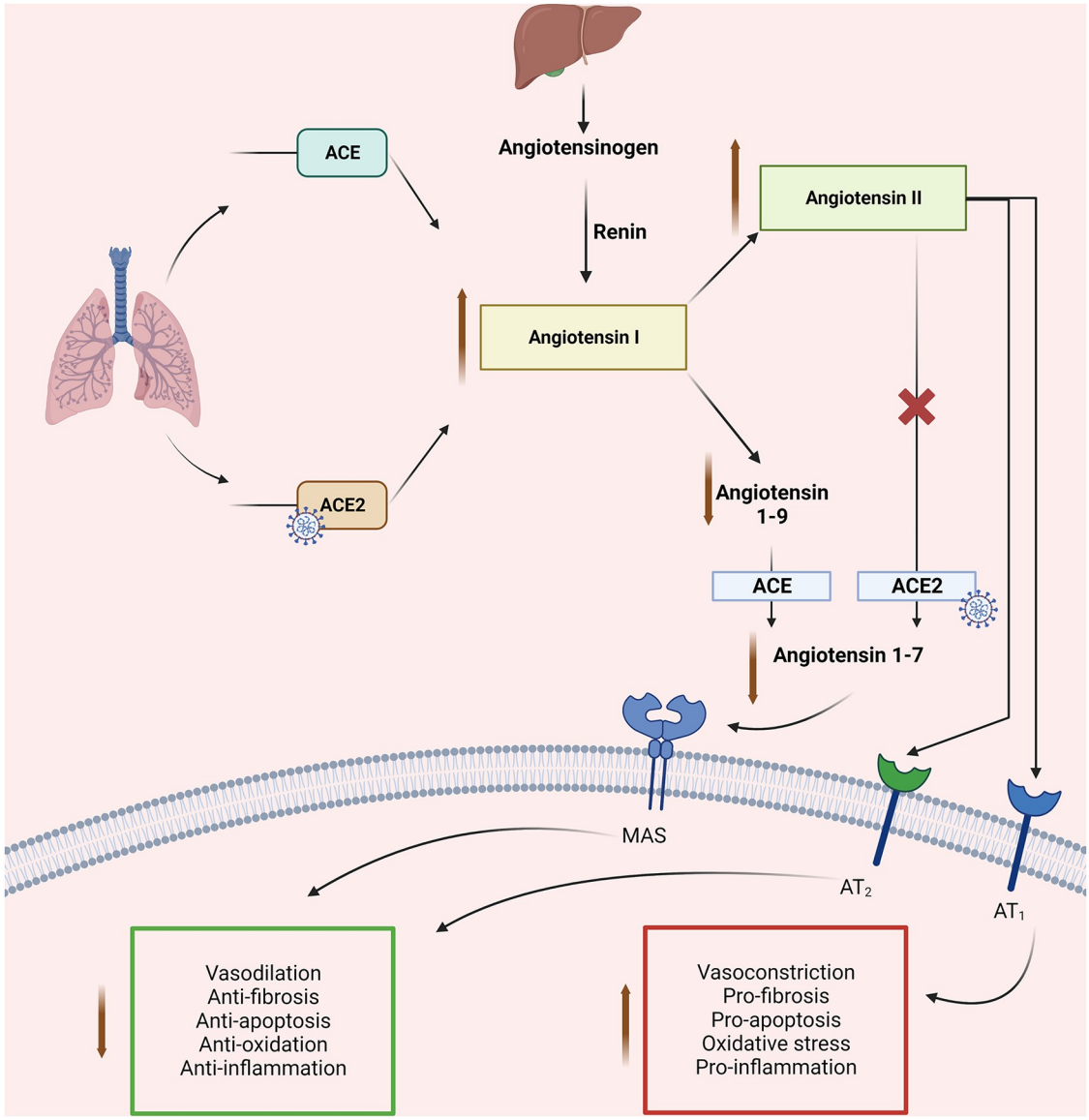

Figure 1. The RAAS system and its dysfunction observed in SARS-CoV-2 infection. SARS-CoV-2 attaches to the ACE2 receptor via its spike protein, preventing the cleavage of Ang II[16]. Consequently, excess Ang II leads to the over-activation of AT1R, resulting in vasoconstriction, hypertension, inflammation, oxidative stress, heart hypertrophy, tissue fibrosis – heart, lungs, kidneys, and liver –, ageusia – loss of taste –, anosmia – loss of smell –, neurological dysfunctions, obesity, diabetes, and skin lesions. This AT1R over-activation is detrimental to the body and may explain the long-term complications of SARS-CoV-2 infection. The wide expression of ACE2 in various tissues increases the likelihood of RAS dysfunction due to SARS-CoV-2 infection, underlying the virus's pleiotropic effects. ACE: Angiotensin-converting enzyme; Ang: Angiotensin; AT1R: Type-1 Angiotensin II receptor; AT2R: Type-2 Angiotensin II receptor; MAS: Mas-related G protein-coupled receptors.

include continuous virus RNA presenting in tissues, persistent immune response after the acute phase of infection, and unrecovered tissue damage. Many studies revealed RNA virus detection in respiratory, cardiovascular, renal, gastrointestinal, and reproductive systems, in addition to the brain, muscles, eyes, and lymph nodes. Elevation of other inflammatory cytokines was also observed. Studies evaluating adaptive immune responses showed alterations in T-cells ratios suggesting immune reactions against viral antigens[16]. In consistent with these results, a study performed endoscopy on irritable bowel disease (IBD) patients to identify viral antigens after acute COVID-19 infection. Several diagnostic tools have been used. Long COVID has been assessed using a standardized questionnaire. Quantitative polymerase chain reaction (qPCR) showed positive viral antigens in 70% of patients. These results are consistent with viral reservoirs theory for long COVID mechanism[17].

A controlled study in Australia has followed individuals with SARS-2 infection for 8 months. Researchers evaluated biomarkers in patients' serum. The results showed IFN-β and IFN-λ1 factors were persistently elevated for 8 months in long COVID patients. Continuous conversion of T-cells into an activated form was also observed. All these results indicated a persistent inflammatory event run by viral reservoirs[18].

By discussing the affected systems solely, the central nervous system has significant importance. It has been hypothesized that SARS-CoV-2 might enter the brain via the circulation or nasal cavity and cause an inflammatory reaction. Other investigations suggest an effect of local microthrombosis in mental impairment. During imaging studies, structural changes have been discovered, and it is linked with certain neurological symptoms, like smell loss, specifically with modifications in grey matter volume. Changes in white matter structure have also been indicated. The role of neurotransmitters – like GABA – has been investigated. Physiologic studies revealed hypometabolism of brain in patients with insomnia. Neuroinflammation may explain smell and taste impairments[6].

The cardiovascular effects could also be explained by an inflammatory response to viral antigens. The response is exacerbated by adipokines released by adipose tissue. The secretion of chemokines results in reactive oxidants' production and nitric oxide synthetase uncoupling. These processes lead to cardiac tissue damage and myocardial fibrosis, thus, affecting ventricular functions, reducing contractility, and increasing stiffness of myocardium. Another mechanism also thought to be involved in long term cardiovascular consequences is delayed immune response. Investigators showed autoantibodies production among patients who had COVID-19. Increased expression of prothrombotic factors and endothelial damage induce the possibility of chronic thrombotic events[19].

Risk factors for long COVID: Insights from observational studies

Studies have investigated several determents as possible risk factors for long COVID. Early studies during COVID pandemic showed a correlation between seriousness of long COVID and intensive care unit (ICU) prior admission, viral load, and the picture of acute illness manifestations (Fig. 2). However, these assumptions have been lately opposed, after identifying SARS-CoV-2 variants. Multiple observational studies looked into patients' medical history as a risk factor for developing long COVID. Asthma, type 2 diabetes, and mental health issues were the most prominent. There is no consensus about age as a main risk factor or secondary to increased morbidities with age. Considering gender as a factor, females were considerably at higher risk of having long COVID, particularly those who are perimenopausal and menopausal. Inflammatory markers, such as D-dimer, CRP levels, and lymphopenia, have been correlated with long COVID risk. However, some studies revealed different outcomes of no influence of biomarkers as a risk factor for long COVID. This inconsistency may be explained by the variations in studies methodologies [1,2].

In a prospective observational study, Legrand, *et al* have classified in their study on hospitalized COVID patients into three subgroups according to symptoms severity. They have not noticed significant differences in 6-month persistent symptoms between the subgroups.[20]

Subramanian, *et al* have investigated, in a retrospective manner, the risk elements correlated with prolonged symptoms in non-hospitalized COVID patients. Analyzing data from 384 137 individuals with COVID-19 infection revealed consistent results with studies mentioned above about the higher risk between females, and individuals with medical morbidities. The most associated medical conditions were chronic obstructive pulmonary disorder (COPD), benign prostatic hyperplasia (PSA), fibromyalgia, anxiety, and depression. However, Subramanian, *et al* mentioned in their study that a role for different ethnic groups on increasing long COVID risk compared with native Americans, Middle Eastern, or Polynesian groups. Smokers, former smokers, and individuals with BMI of 30 kg m^{-2} and greater were also at increased risk[21].

The molecular basis of long COVID

Immunology and virology

The etiology of long COVID is yet insufficiently understood. Particularly, in convalescent patients after a mild acute SARS-CoV-2 illness without any evident organ damage, it seems conceivable that the persistence of inflammatory and autoimmune condition may be responsible for the of prolonged diverse symptoms[22]. Various studies have reported increased levels of autoantibodies in long COVID[23], including autoantibodies to ACE2 – the receptor for SARS-CoV-2 entry[24], muscarinic M2 receptor, β2-adrenoceptor, and angiotensin II AT_1 receptor[25]. Molecular imitation between SARS-CoV-2 S glycoprotein peptides and various human antigens, has also been linked to autoimmunity[26,27]. Thus, some individuals have high levels of other autoantibodies, including those that target body tissues, including anti-nuclear antibodies (ANA), immunomodulatory proteins – such as cytokines, chemokines, and complement components – and organ systems[28].

However, an in-depth study by Glynne, *et al* found that autoantibodies were not a significant factor in protracted COVID[29]. Immune dysregulation plays an essential role in long COVID, including, decreased CD4+, CD8+, and effector memory cell counts and presence of exhausted T cells, with increased PD1 expression on central memory cells, which persisted at least 13 months[30]. In addition, studies have found highly activated innate immune cells, a deficiency of naive T and B cells, and enhanced type I and type III interferons expression – interferon-β (IFNβ) and IFNλ1[18].

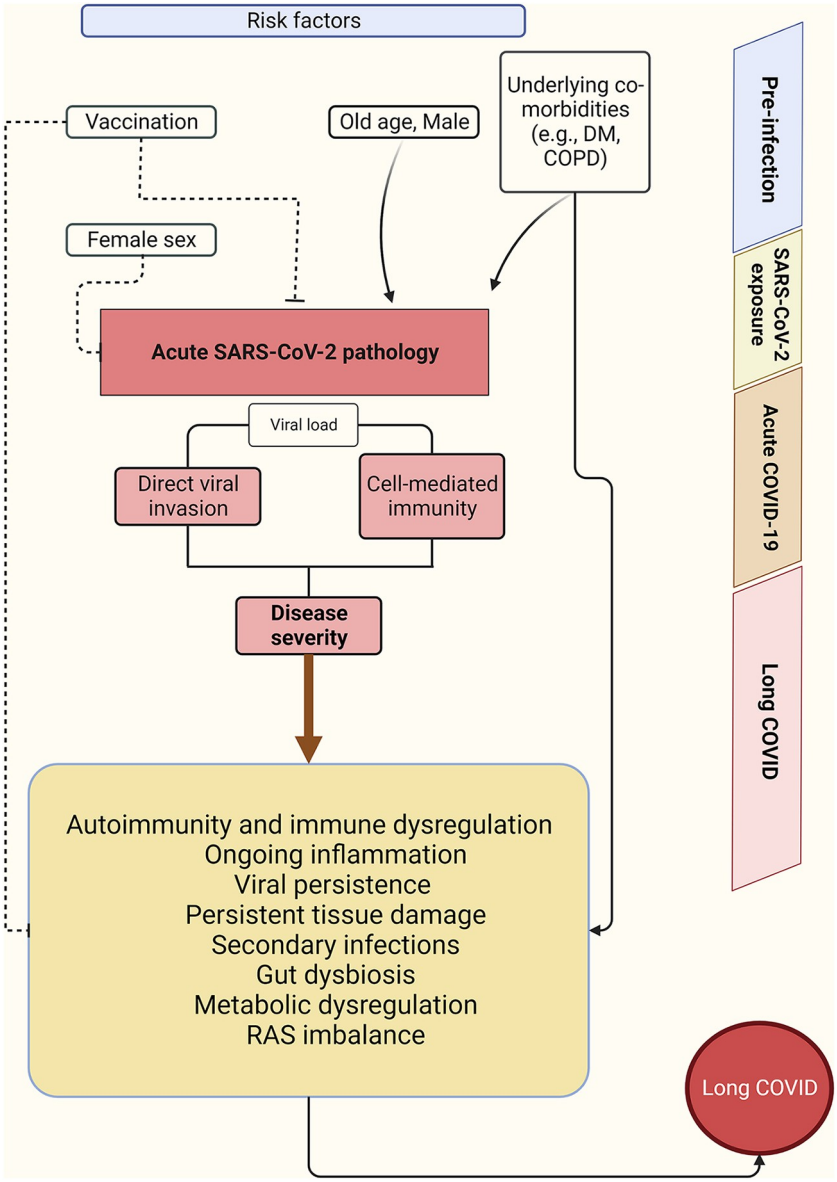

Figure 2. The suggested risk factors and consequential pathophysiological implications for developing long COVID. Advanced age, pre-existing comorbidities, and incomplete COVID-19 vaccination have been established as significant risk factors for severe acute COVID-19, subsequently elevating the likelihood of experiencing long COVID. Changes in clinical parameters, including immunoglobins, inflammation cytokines, and microbiome profile, may serve as indicators of the progression of long COVID. Additionally, such predisposition could also influence the recovery process.COVID-19: Coronavirus Disease 2019; RAS: renin-angiotensin system, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Long COVID patients had higher levels of non-classical monocytes, activated B cells, double-negative B cells, and IL-4- and IL-6-secreting CD4+ T cells and lower levels of conventional dendritic cells and exhausted T cells, according to a large study comparing them to healthy population and infected individuals without post COVID symptoms[31].

A recent publication demonstrated prolonged elevation of CCL11, which is linked to cognitive dysfunction, and other studies have discovered elevated levels of cytokines, specifically IL-1, IL-6, TNF, and IP10[32–34]. Viral persistence has been suggested as a potential driver of long COVID symptoms, with viral proteins and RNA found in various organs[35]. A study found that circulating SARS-CoV-2 spike antigen was found in 60% of 37 patients with long COVID up to 1 year after the diagnosis of acute illness, suggesting a reservoir of active virus or components[36]. Gastric biopsies have also indicated the presence of virus, suggesting a persistent reservoir in some patients[30,35].

It has been demonstrated that long COVID patients have reactivated viruses, such as HHV-6 and EBV[37,38], which cause fragmented mitochondria and adversely impair energy metabolism. In patients with long COVID, EBV reactivation has been linked to fatigue and neurocognitive impairment, according to a recent preprint[37–39].

Epigenetics

Epigenetic alterations refer to changes in gene expression and cellular phenotypes that are not caused by changes in the underlying DNA sequence, but these alterations can be influenced by various factors, including environmental exposures and viral infections[40].

One emerging area of research is the role of epigenetics in long COVID. Studies have found that SARS-CoV-2 infection can induce epigenetic alterations in the host chromatin and epigenome. These alterations may have long-term effects on gene expression and cellular function, potentially contributing to the development of the disease[22].

A study by Balnis, *et al*[41] provided the first known proof that DNA methylation (DNAm) modifications in circulating leukocytes persist even after recovery from an acute COVID-19 illness. Of the 1505 previously identified acute illness-induced differentially methylated regions (DMRs), they discovered 71 regions that remained differentially methylated. Significant telomere shortening and decreased *Angiotensin II* (*ACE2*) gene expression are observed in long COVID patients[22,42]. Further, it is also suggested to be linked to changes in the gut flora, which may be responsible for persistent neuropsychiatric and respiratory symptoms as well as exhaustion[22]. The gut microbiome's function in epigenetic regulation indicates that its changes may also be implicated in long-term epigenetic consequences[43].

A Swedish study by Huoman, *et al*[44] found epigenome-wide variations in the DNA patterns of individuals who had recovered from a mild-to-moderate COVID-19 disease. In an experimental SARS-CoV-2 infection model that included 66 genes, six of which – *TP53, INS, HSPA4, SP1, ESR1*, and *FAS* – were present in matching *in vitro* investigations, different DNAm patterns were able to identify COVID-19 convalescents from uninfected controls. DNA methylation patterns imply that recovery from SARS-CoV-2 infection leaves long-lasting epigenetic changes that could be included in the mechanism of the disease. Several pathways that were discovered to be epigenetically altered in long COVID patients, such as the ACE2 receptor, muscarinic receptors, and histamine signaling pathways, are important for the clinical presentation of the syndrome[29]. The pathways mediated by the muscarinic receptors CHRM1&3 are involved in smell perception and have been reported to be epigenetically altered[45]

Future research should ascertain if these epigenetic alterations are due to targeted viral hijacking to circumvent host protection or host-induced defensive antiviral mechanism.

Systemic manifestations of long COVID

Common symptoms in people with long COVID are profound fatigue, breathlessness, cough, chest pain, palpitations, headache, joint pain, myalgia and weakness, insomnia, pins and needles, diarrhea, rash or hair loss, impaired balance and gait, neurocognitive issues, including memory and concentration problems, and worsened quality of life (Table 1)[46]. In people with long COVID one or more symptoms may be present.

Respiratory manifestations

Most patients present with normal lung function during follow-up after recovery from acute COVID-19. However respiratory complications were the most prevalent and reported following an acute SARS-COV2 infection. Hospitalization during acute COVID-19 has been the best predictor so far of post-COVID-19 lung sequels, which mainly include – from most to least common: mild to moderate decreased diffusing capacity of the lung for carbon monoxide (DLCO), a restrictive pattern evident as reduced forced vital capacity and an obstructive pattern up to 6 months following hospital discharge. DLCO less than 80 was associated with severe SARS-CoV-2 cases, in addition to reduced maximum inspiratory, expiratory, and total lung capacities[46–49]. These abnormalities were of the same prevalence at 12-month post-infection except for the restrictive pattern which decreased in prevalence after 6 months following the infection[49]. Dyspnea and cough were also a part of the most commonly reported persistent symptoms following acute infection[50]. Reduced inspiratory muscle strength, sedentary behavior, and impaired exercise tolerance were also reported[51]. The SARS-CoV-2 nucleocapsid protein is approximately similar to that of SARS-CoV-1. A 12-months follow-up of patients who have recuperated

Table 1

Predominant and common clinical features and symptoms of long COVID

Clinical features/Symptoms	Description	Further notes
Fatigue	Persistent and debilitating tiredness.	Differentials include anemia, and electrolyte imbalance which must be ruled out
Brain Fog/Cognitive issues	Problems with memory, focus, and mental clarity. Also patients report headaches and insomnia	Psychological issues needs to be taken care
Cardiopulmonary	Cough, low-grade fever, and shortness of breath	
GI disturbance	Abdominal discomfort, diarrhea, constipation, and nausea	Maybe due to drugs associated with acute COVID-19 infection
Joint and muscle pain	Aches and pains in joints and muscles, weakness	
Skin rashes	Vesicular, maculopapular, or urticarial; development of skin rashes or lesions that arise as a long-term consequence of acute COVID-19 infection	
Multisystem inflammatory syndrome/post COVID autoimmune syndrome	Fever, gastrointestinal symptoms, rash, chest pain, and palpitations	Elevated levels of markers of inflammation.
Genito-urinary symptoms	Proteinuria, haematuria, anddevelopment of kidney injury	Endothelial dysfunction, coagulopathy, complement activation, direct effect of virus on kidney, sepsis, and multi- organ dysfunction contribute to the development

from SARS-CoV-1 illness, has shown chest X-ray abnormalities in more than 1/4th of the individuals. The degree of functional lung impairment, and the severity of imaging abnormalities were closely correlated[52].

On lung computed tomography (CT) scan, air trapping, ground-glass opacities (GGOs), reticulation, and traction bronchiectasis. Interlobular and interlobular septal thickening were the commonest abnormality identified; these all are findings related to pulmonary fibrosis. About 33% of SARS-CoV-2 survivors were found to develop significant pulmonary fibrosis, which was attributed to the following:[49,51–53]

1. Prothrombotic and proinflammatory damaging state induced by the virus, leading to thrombus and emboli formation.
2. Pro-fibrotic signaling molecules upregulation, including transforming growth factor-beta (TGF-β).

These abnormalities were persistent even a year after the acute illness[49]. These complications paired with secondary bronchopneumonia comprise a major contributor to the increased chance of morbidity and death among SARS-COV2 patients[52]. These fibrotic changes have also been recognized for the cough reflex increased rate up to 4 months following the infection[54].

Cardiac manifestations

Cardiac symptoms and inflammation beyond acute infection have been postulated to be the result of 2 mechanisms:[19,55,56]

1. Persistence of viral reservoir within the heart beyond the time of acute infection induces a chronic inflammatory reaction which could possibly be exacerbated by obesity-related increased perivascular adipose tissue by secreting adipokines along with normal T cells production, chemokines, and reactive oxygen species production lead to tissue damage and cardiac muscle fibrosis, which in turn, increase myocardial stiffness and decrease its contractility, perfusion, and ventricular compliance, all leading to possible arrhythmias. About 62.5% of patients taking part in an autopsy study conducted on 39 COVID-19 cases were found to have the virus in their heart tissues.
2. Molecular mimicry – i.e., an autoimmune reaction to cardiac cellular antigens similar to those of SARS-COV2. Some of these autoantibodies to humeral and tissue antibodies have been identified.
3. RAS over-action due to the high expression of ACE2 in patients, which leads to electrolyte and fluid dysregulation, increased risk of hypertension and thrombosis due to excessive vasoconstriction. Eventually, increased cardiac afterload and cardiac dilatation will result.
4. Respiratory system dysfunction and failure leading to hypoxic injury.

About 20% of patients' experience chest pain and 14% reported palpitations at 3 months following the infection. Dyspnea have also commonly reported in patients having myocardial ischemia, heart failure, arrhythmia, and pulmonary emboli[57,58]. Myocarditis, a common etiology of sudden cardiac death in an athlete, is commonly known to be a viral infection sequelae[57]. Its prevalence has been low, some even considered it to be overestimated even in cases with predominant cardiovascular symptoms, due to lack of comparable control groups in multiple studies[59].

Postural orthostatic tachycardia syndrome (POTS) is a pattern of dysautonomia possibly due to molecular mimicry, has been reported to occur concurrently with acute COVID-19 or even months after infection resolution. Patients usually complain from tachycardia, palpitations, and dizziness upon changing their position from recombinant to upright[59,60]. It has been proposed that post-COVID tachycardia syndrome is different, and is a separate entity from POTS[60]. Pulmonary hypertension and right ventricular dysfunction have also been reported in severe cases[55].

Arrhythmia and ECG changes were varied, however most patients had similar ECGs to their baseline ECGs upon hospital admission. It has been found that a similar rate of atrial fibrillation/flutter was shared by both influenza and COVID-19 with results attributing it to severe systemic disease. Mild pericardial effusion can be fairly common in the long COVID patients, however frank pericarditis is found to be infrequent[59].

CNS, sensory neurons, and neuropsychiatric manifestations

The neuropathological mechanisms of post COVID disease have not been well studied; however, most relate them to the mechanisms recognized and reviewed of acute COVID-19, such as oxidative stress and ischemic neuronal injuries, in addition to coagulopathy and endotheliopathy, leading to dysfunctional blood–brain barrier. Most frequent symptoms described were fatigue, headache, and attention disorder, in addition to ageusia, anosmia, memory loss, hearing loss, dizziness, and stroke[19].

The olfactory nerve has been postulated to be one of the pathways by which the virus reaches the brain[61]. These pathways are believed to be mediated by ACE2R and proteases found in the specialized neuroepthelium of the olfactory nerve supporting cells which contains odor sensing cilia thus when disrupted leads to anosmia. Other sensory nerves in the body have been also associated with the SARS-CoV-2 virus as it has been isolated from the trigeminal nerve sensory ganglia[54,62]. It has also been suggested that the virus infects the vagal sensory neurons responsible of the cough reflex leading to brainstem hyper-stimulation and an increased rates of persistent cough following the infection.[54]

Altered perception of odor and taste is one of the most recognizable manifestations of acute COVID-19 and long COVID only second to fatigue, which was the commonest, while most do recover from it in a matter of weeks, about 10% persist beyond acute infection resolution into a chronic state. Many patients reported symptoms of anosmia, hyposmia, parosmia, and phantasomia, which mostly manifested as offensive or chemical smells. Food flavor is a combination of both taste and smell sensory senses, if any of them is disrupted the flavor is changed. Ageusia, hypogeusia, and dysgeusia, mostly relating to metallic repulsive tastes, have also been commonly reported. These changes eventually lead to limiting food options or avoiding it altogether with subsequent weight loss as a result[63,64].

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is a complex complaint possibly resulting from an immune response change to stress or infection like SARS-COV2, which has contributed to increasing ME/CFS prevalence. However, in most cases the infectious agent cannot be identified or isolated.

The illness is described as chronic persistent fatigue unrelieved by rest, unrefreshing sleep, and post-exertional malaise, which is usually associated with orthostatic intolerance, autonomic dysfunction, or CNS manifestations, such as cognitive impairment and hyperalgesia. The illness varies from mild to severe as ¼th of these patients are bed-bound[65–67].

Long term brain damage as a sequelae to SARS-CoV-2 infection has been supported by growing verifications. This damage possibly leads to cognitive impairment and psychiatric presentation regardless of the disease acute phase severity[68]. Patients with COVID-19 were noted to have an increased risk of developing neuropsychiatric diseases in comparison to other infectious disease. The risk remained higher even 2 years following the infection[69] Fatigue and depression were more frequent in patients with long COVID than those with post-sepsis which further highlights the virus's effect on the nervous system[70].

Most patients' psychiatric symptoms have manifested after COVID-19 respiratory symptoms have appeared; however, many have already had pre-existing psychiatric diagnosis or predisposing factors. Middle aged males were the main population that developed new onset psychiatric symptoms[68,71]. The commonest was new onset of bizarre behaviors that were previously not present, such as use of eccentric language. Agitation and aggression were also of a higher prevalence than depression and anxiety[68]. Fatigue, sleep disturbances (mainly insomnia), and post-traumatic stress disorder (PTSD) were also commonly noted[72].

Cognitive impairment, affecting patients' memory, attention, concentration, and learning capacity, were commonly reported and many of those patients mainly had deficits in the area of executive functioning but had normal alerting and orienting abilities. However, symptoms seemed to improve over a period of 6–12 months. Long COVID-19 had an impact on patients' life, reducing its quality especially those who suffered cognitive impairment as many of them has difficulty working, driving, and following simple tasks[69].

Vascular manifestations

SARS-CoV-2 induces a pro-inflammatory, pro-thrombotic state in the body leading to a disseminated intravascular coagulation, which especially affects the tissues of the lungs, heart, and the nervous system, which are highly sensitive to ischemia[53].

SARS-CoV-2 enters the endothelial tissues through ACE2 receptor causing its downregulation on the endothelial surfaces leading to angiotensin II accumulation in the blood, which induces vasoconstriction and pro-inflammatory effects. This excessive activity of angiotensin II, the production of interlukins 1 and 6, increased capillary permeability all lead to a pro-thrombotic state[53].

Additionally a persistent endothelial activation, a decrease in plasma fibrinolytic potential and an increase in the pro-thrombotic factors beyond the acute infection has also been noted, such as factor VIII, prothrombin, plasminogen activator inhibitor-1, Von Willebrand Factor, endogenous thrombin potential (ETP), and D-dimer, 4–12 months following acute infection[53,73,74]. 73% of patients had elevated erythrocyte sedimentation rate and CRP. 30 days after hospital discharge, patients had a 2.5% cumulative incidence of arterial and venous thrombosis. Prolongation of this pro-thrombotic status leads to systemic damage in these patients[74].

Renal system manifestations

The kidneys during acute COVID-19 are more prone to be affected if the patients are hospitalized or have chronic illnesses. The mechanism of acute kidney injury (AKI) can be either direct or indirect[75].

1. Direct injury as a sequelae of viral entry, complement activation and inflammation.
2. Indirect injury through sepsis, nephrotoxic drugs, and the pro-thrombotic state of the body.

Persistence of these effects, recurrent injuries to the kidneys following recovery and the severity of the infection itself increase the risk of chronic kidney disease (CKD), which in turn, heighten the risk of needing a kidney replacement therapy (KRT). The relationship between CKD and COVID-19 is believed to be bidirectional as each increase the risk of the other. Six months following recovery from acute COVID-19, about 35% of patients who have had an AKI episode during the infection and 13% of those who didn't experience AKI were found to have a decreased kidney function – estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m^2 .[75–77]. However slower renal recovery and greater decrease in eGFR was found in patients with COVID-19 associated AKI than those with AKI alone[78].

Viral entry into the kidney is mainly through the ACE receptors and the transmembrane protease, serine 2 (TMPRSS2) expressed by the proximal tubules and collecting ducts epithelial cells and to a lesser extent through receptor CD147 found on the epithelia cells of proximal tubules[76]. Patients who developed mainly stage 2 or stage 3 AKI or unresolved kidney injury are associated with a higher risk of morbidity and mortality following hospital discharge[79].

Gastrointestinal tract and endocrine manifestations

COVID-19 affect the gastrointestinal tract (GIT) through ACE2 receptors, which are widely expressed throughout the whole GIT system leading to malabsorption, disturbance in intestinal secretions, and uncoordinated gut-associated lymphoid tissue (GALT) immune response[62]. It also induces hyper-inflammation through reducing butyrate-secreting bacteria leading to potential dysbiotic pattern of increased pathobionts. It also decreases anti-inflammatory responses of *Faecalibacterium* and *Bifidobacterium* while increasing pro-inflammatory lipopolysaccharide- producing microbiota[65,80,81]. An increase in gut wall permeability allows bacterial byproducts to enter circulation, and anabundance of bacterial taxa has been associated with chronic fatigue syndrome pathogenesis[65]. SARS-COV2 also causes hepatic steatosis through its action on hepatocytes endoplasmic reticulum which in turn induces lipogenesis[80].

The virus also impairs insulin secretion through damaging pancreatic β-cells[76]. Diabetes can develop due to viral direct damage during the acute or the post-acute period of COVID-19 infection or it can be steroid-induced as patients with severe COVID-19 receive an 8–10 days steroids, in addition to patients suffering from pulmonary dysfunction sequelae. Abrupt cessation of steroids led to acute adrenal insufficiency. Patients with pre-existing autoimmune disease have a higher risk of developing long COVID-19 sequelae[82].

Musculoskeletal manifestations

COVID-19 can cause muscle injury either directly or indirectly[83–85] – directly by viral direct muscular invasion through ACE and TMPRSS2 receptors, which are almost expressed in all body tissues; indirectly due to the pro-inflammatory state of the body and increases cytokines, such as interferon gamma, C-reactive protein, IL-6, IL-2, IL-10, and tumor necrosis factor α. It can also be due to hypoxia, electrolyte imbalance, and steroid drugs. COVID-19 can induce epigenetic modifications, thus reprogramming macrophages into a long-term pro-inflammatory state. Reduced muscle activity, restriction of movement, and poor nutritional status were also suggested to play a role in its pathogenesis.

These mechanisms of injury will cause muscle fiber destruction, hindering their regeneration, and eventually leads to muscle fibrosis with subsequent muscle weakness and persistent pain. Worse physical performant was reported in patients who suffered severe COVID-19 infection in comparison to those who have experienced a mild to moderate disease, which has also shown to affect quality of life. However, muscle function and mass has been shown to improve 12 months following the infection. A reduction in diaphragm muscle thickening ratio and respiratory muscle weakness have also been implicated a higher risk of developing muscle sequel has been found in obese patients[83-85].

Previously mentioned cytokines in addition to granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10) and monocyte chemoattractant protein-1 (MCP-1) are well known mediators in the bone turnover process. Thus, the pro-inflammatory state of the body can induce bone loss through osteoclasts upregulation while reducing osteoblasts activity thus disrupting the balance between them ultimately leading to an osteosarcopenic state. It could also induce arthralgia and osteoarthritis in addition to tendon degeneration.[84,85].

Reproductive system manifestations

Testes have a high expression of ACE2 receptors, mainly in leydig cells, sertoli cells, and spermatogonia. While spermatogonia and spermatozoon mainly express TMPRSS2. This expression varies with age and is highest in men at their thirties making testes a possible target tissue for SARS-COV2 leading to orchitis and infertility. However high co-expression of ACE2 receptors and TMPRSS2, which COVID-19 viral entry into cells is highly dependent on, is low making the possibility of SARS-COV2 infecting testicular cells less likely. Spermatogonia express high levels of TMPRSS2, but low levels of ACE2. While sertoli cells express high levels of ACE2, but low levels of TMPRSS2[86–88].

In post-acute COVID-19, many male patients, especially severe cases, were diagnosed as oligocrypto-azoospermic, to a lesser extent some patients were diagnosed with azoospermia and the least prevalent was oligospermia. Moreover, 76.7% of patients' semen fluid revealed the presence of IL-8. These changes seemed to persist for at least 3 months following recovery[88].

Sperm count was shown to be decreased and only returned to normal 5 months following recovery, however decreased sperm motility and morphology was found to reverse and increase 3 months following the infection[88]. Decreased levels of testosterone can impair spermatogenesis and fertility potential; it was found that following the infection the level of testosterone decreased and the level of LH/FSH increased compared to the controls. COVID19 has also an effect on leydig cells leading to their reduction and secretory dysfunction, it also has also been shown to decrease the levels of dihydrotestosterone. The mechanism of these effects have mainly been attributed to increased immune reaction to reproductive tissue inflammation[88].

ACE2 expression was found in the ovaries, uterus, vagina, and placenta. Female ovaries mainly had ACE2 expression in the hilus with minimal expression in the cortex and its expression was found to be independent of age. Oocytes are the main site for ACE2 and TMPRSS2 co-expression, while granulosa cells had partial co-expression. The ACE2 receptors are present in the testes and to a lesser extent in the ovaries suggesting a higher susceptibility for males' gonads to be affected by COVID-19[86]. COVID-19 can cause infertility or abortions through reducing oocyte quality, ovarian function, and endometrial epithelial cells. Estrogen has been found to have a protective effect against SARS-COV2 virus because estrogen receptors are present expressed by immune cells and play a role in innate/adaptive immunity, they have also been shown to modulate ACE2 receptors expression. Both progesterone and estrogen have an anti-inflammatory effect protective against SARS-COV2, which explains the higher rates of severity, morbidity and mortality amongst men[89].

DPP4 (cluster of differentiation 26) expressed by both male and female gonads is now considered a potential route for SARS-COV2 entry into host cells. This co-receptor expression plays an important role in polycystic ovary syndrome (PCOS) which makes them more susceptible to getting the infection and suffering its sequela such as infertility[86].

Approaches and challenges in diagnosing and managing long COVID

Diagnostic results are often normal in long COVID patients. However, biomarkers, inflammatory profile, such as D-Dimer for pulmonary dysfunction, C-reactive protein levels, TNF-α, IL-6, IL-1, IL-10, and lactate dehydrogenase (LDH), immune markers, blood tests, saliva tests, erythrocyte deformation, sex-specific lipid profiles can all be used to predict the presence of long COVID but none of them is specific enough to give a definitive diagnosis of the case. Clinical evaluation of patients presenting with long COVID starts with documentation of the existing problem – its improvement or deterioration – and also documentation of new problems, if any (Fig. 3). Imaging like X-ray, computed tomography angiography (CTA), dual-energy CT scan for pulmonary embolism detection, and MRI for the brain can all assist the diagnosis of long COVID[5,30,90,91].

Spirometry to assess respiratory capacity, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), vital capacity (VC), FEV1/FVC ratio, peak expiratory flow (PEF), and the inspiratory vital capacity (IVC)[91]. A comprehensive systemic-based assessment through medical history and examination is crucial[2]. There are no particular treatments for long COVID and a multi-disciplinary process to identify, refer, and treat these patients, is usually required due to the wide variety of possible affected systems, symptoms, and resultant illnesses[5,30,90]. Long COVID can cause significant deterioration in the patients' quality of life and rehabilitation programs are required in some patients, such as cardiopulmonary-rehabilitation programs were patients are required to do light aerobic exercises, which increase in difficulty with time to improve symptoms of dyspnea and fatigue[91].

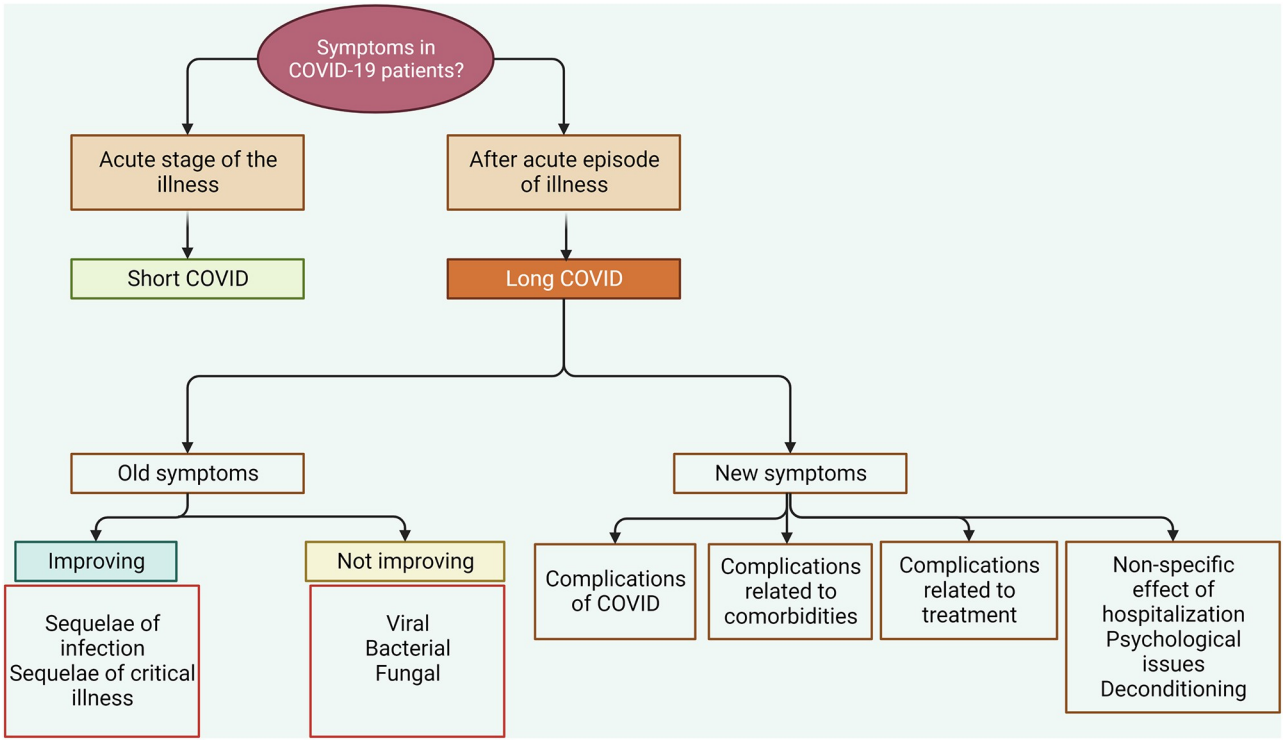

Figure 3. Algorithm demonstrating how to approach a patient with long COVID[90].

For pharmaceutical treatments, paracetamol and non-steroidal drugs can be used to manage specific symptoms, such as fever, other drugs used in similar conditions to those faced with long COVID can be re-proposed, but further research is still needed; however, no medication specific to long COVID has yet been proposed[1]. Several guidelines have been released for the management of long COVID however they are still not reviewed and a big practical gap still remains[2].

Antihistamine treatment has been suggested as part of the management of mast cell activation syndrome (MCAS) resulting from the immune disturbance induced by SARS-CoV-2 infection. Dietary supplements, such as vitamins and minerals, which contain anti-inflammatory and anti-oxidative components have also been suggested as potential treatment choice[2]. Some trials showed that olfactory dysfunction improved upon using antiinflammatory, neuroprotective agent palmitoylethanolamide, luteolin (PEA□LUT), and vitamin D3[92].

Conclusion

Future trends indicate that there will be an increase in the number of cases with long COVID. Regarding the existing information, long COVID can develop in any patient who had a prior COVID-19 infection of varying severity, however a greater likelihood is associated with severe cases. The epidemiology of long COVID remains not fully established, due to diverse classifications and clinical manifestations. Consequently, long COVID can have a wide spectrum of clinical presentation and could affect various body organs. Furthermore, the diagnostic criteria are ambiguous, and plausible mechanisms and successful management of this condition require additional research. Researchers have put several presumptions regarding long COVID etiology and mechanism, especially as this disease has a multi-organ involvement. Nevertheless, the definite pathophysiology of the disease is not sufficiently understood. Moreover, autoimmunity and inflammatory reactions seem to be a promising player in the course of long COVID symptoms. Although, it is still considered a matter of uncertainty and requires conclusive evidence. One of the emerging area of research is the role of epigenetics in long COVID. Just as, various pathways were reported to be altered epigenetically including, ACE2 receptors, muscarinic receptors, histamine signaling pathways, and CHRM1&3 that are involved in smell perception. Future research should ascertain if these epigenetic alterations are due to the viral effect itself or host-induced defensive mechanism.

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