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Long-Term Consequences of Covid-19: A Scope of Analysis on the Ongoing Physical and Mental Health Complications

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ABSTRACT:
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 2019 (COVID-19), has spread across the world. Despite vaccination efforts, SARS-CoV-2 has infected over 1.1 million individuals in the United States alone, with a new wave of increasing cases partially due to novel variants, such as the Delta variant of the virus, which are more easily transmissible. The clinical presentation of COVID-19 has been shown to vary widely, often with respiratory complications as a major feature. SARS-CoV-2 is notable in that a number of patients have gone on to develop long-term complications of the virus. Beyond initial reports of patients feeling fatigued for months following initial infection, long-haul COVID-19 has come to represent wide complications and sequelae of symptoms that may arise. These receptors are expressed in epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, pancreatic β cells, and renal podocytes suggesting that direct tissue damage may be a primary mechanism of the presentation of SARS-CoV-2 infection, which may also contribute to its longer-term complications. Early data on in the pandemic revealed that endothelial cells had high expression of ACE2 and that COVID-19 infection led to substantial alteration to the integrity of the vessel barrier and promotion of a procoagulative state. Although SARS-CoV-2 can have wide-ranging impacts throughout the body, COVID-19 remains predominantly a respiratory illness. The physical and mental health conditions associated with COVID-19 includes neurological and psychiatric symptoms include fatigue, weakness after exertion, cognitive complaints, sensorimotor symptoms, headaches, insomnia, depression. There have been many long-term pulmonary complications described following COVID-19 infection. The lung diseases are prevalent medical conditions among COVID-19 patients globally, and patients with asthma and COPD are highly susceptible to getting infected. COVID-19 mainly causes respiratory tract infections in humans. The secondary fungal and bacterial infections in the lungs have been diagnosed earlier in patients affected by other coronaviral diseases. The early identification of infection and initiation of treatment measures can lower the COVID-19 associated mental health complications.

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Introduction

Coronavirus disease 2019 (COVID-19) has escalated into an unprecedented global pandemic since the first case was identified in December 2019. By June 20th 2022, more than 535 million individuals were infected with over 6.3 million deaths worldwide according to World Health Organization (WHO) [4]. Apart from the severe morbidity and mortality in the first few weeks after infection, up to 70% COVID-19 survivors may experience long-term medical complications [5-7]. The lingering symptoms after COVID-19 infection can last weeks to months, severely reducing the quality of life long after patients become virus-free. Such symptoms are generally reported as "long COVID" in common literature.

With so many affected patients, long COVID posts a global health challenge for the society. In the US, by fall 2021, cumulative loss from direct economic losses in conjunction with mortality, morbidity and relative metal health complications of COVID-19 is estimated at $16 trillion. The substantial burden of the pandemic should not be neglected. In just two years, a large volume of evidence has been accumulated on the pathological manifestation, treatments and preventative measures of long COVID [1]. It is necessary for health professionals and the general public to gain more knowledge about the disease. Therefore, this review will present our current understanding of long COVID and highlight the potential management strategies and therapeutics[1-4].

Acute COVID-19 stage generally refers to the initial five weeks after SARS-CoV-2 infect patients. When SARS-CoV-2 first enters the host respiratory tract, it initiates infection through the binding of the spike protein with Angiotensin-converting enzyme II (ACE2) receptor, and then utilizes transmembrane protease serine 2 (TMPRSS2) to enter host cells. SARS-CoV-2 hijacks the host cellular machinery for viral RNA replication and protein production. SARS-CoV-2 load usually reaches its peak upon symptom onset within the initial weeks of infection, and first becomes detectable by reverse transcription polymerase chain reaction (RT-PCR) within the first week of infection. At the peak of infection, a patient could carry 10^9 to 10^{10} virions.

Acute COVID stage usually lasts five weeks till the viral load gradually declines from its peak to undetectable. During this period, viral infection often disables host cellular machineries, leading to functional impairments, even cell death. Subsequent cytokines recruitment often contributes to systematic hyperinflammation and leads to progression of thrombosis even multi-organ failure and death [2, 13]. Majority of the confirmed cases (81-45%) were reported to be asymptomatic or mild disease at time of diagnosis. Approximately 25% of the initially asymptomatic individual would develop symptoms throughout COVID-19 acute stage. The Chinese Center for Disease Control and Prevention reported 14% of the COVID-19 patients were hospitalized with severe illness including dyspnea and 5% were reported as critical cases with disease progression to respiratory failure, shock, or multi-organ impairment [16]. Additionally, critical or fatal risk of SARS-CoV-2 varied by age, pre-existing comorbidities and vaccination status. Pathophysiology of COVID-19 and its relevant biological disease course have been reviewed comprehensively elsewhere .

About three weeks after initial detection by RT-PCR, the viral load becomes undetectable. This marks the end of acute COVID, but also the start of post-acute stage. COVID-relevant health issues could linger around as long COVID for years even in patients who are asymptomatic during the acute stage. Survivors of virus infections are at risk of developing physiological complications and multi-organ impairment. The subacute and sequelae effects of SARS-CoV-2 infection are called various names, such as "long COVID", "post-acute COVID syndrome", "post-COVID-19 condition" and "long-haul COVID-19". In response to the absence of a consensus definition for long COVID, WHO has made a clinical case definition to the public in delineating long COVID. "Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis[5-10]." The National Institute for Health and Care Excellence (NICE) defined post-COVID-19 syndrome as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

It is estimated that 31%-69% of COVID-19 survivors will experience long COVID symptoms after initial recovery from SARS-CoV-2 infection . Generally, initial symptoms of long COVID symptoms include

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fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnea (21%), anxiety (27%), chest pain, and arthralgia (18%) . Among the UK population, fatigue is most prevalent among long COVID patients (51%), followed by dyspnea (35%), arthralgia (25%) and concentration difficulties (25%). Correspondingly, a recent meta-analysis of 36 studies identified fatigue, cognitive impairment, joint pain, anxiety, and depression as primary clinical symptoms of long COVID. A massive international survey found fatigue, malaise and cognitive impairment as the most prevalence symptoms experienced among individuals with reported long COVID. Furthermore, cognitive related symptoms were reported to develop at later long COVID stages. While many cases were initially reported in hospitalized COVID-19 patients who experienced severe symptoms during the acute stage, long COVID symptoms have also been documented in non-hospitalized or asymptomatic individuals [24]. Approximately 30% of non-hospitalized COVID-19 patients reported lingering symptoms 2 months after initial infections [25]. Similarly, less than 1% of COVID survivors achieved complete recovery at 80 days after infectionAs a respiratory virus, SARS-CoV-2 infection leads to respiratory system dysfunction in long COVID. SARS-CoV-2 initially infects the alveolar epithelium, and induces chronic inflammation responses that trigger sustained production of inflammatory cytokines and reactive oxygen species (ROS) . Additionally, disruption of cellular integrity activates fibroblasts to deposit collagen and fibronectin, leading to fibrotic changes to lung tissue. In the long-term, viral-induced complement activation and subsequent disruption of coagulant pathways favor the development of prolonged inflammation and hypercoagulable state, predisposing the patient to the risk of thrombosis . National data from UK suggested that 36% of long COVID individuals experienced shortness of breath to a certain extent. 26% of long COVID individuals develop signs and symptoms of lung impairment. Respiratory abnormalities involving changes in total lung capacity and airway function have also been reported following COVID-19 infection [32]. In addition, dyspnea is prevalent in COVID-19 survivors along with other respiratory symptoms, including chronic chough and reduction in exercise capacities[11-16].

Many long COVID patients also experience cardiovascular complications. The abundance of ACE2 receptors on cardiomyocytes provides a direct route for SARS-CoV-2 infection. Chronic inflammation of the cardiomyocytes can lead to myositis and cell death. Prolonged inflammation and cellular damage prompt fibrotic changes and reduce cell adhesion, all of which could lead to arrhythmia and the development of coagulopathy. In addition, inflammation of the autonomic nervous system might progress to postural orthostatic tachycardia syndrome (POTS). Persistent myocardial inflammation and increased cardiac troponin level are commonly present in COVID-19 patients 2 months after diagnosis. Evidence have suggested increased risk of cardiovascular compilations following SARS-CoV-2 infection, even among non-hospitalized patients. In particular, cardiovascular risk was associated with the severity of infection during acute COVID-19 [35]. Correspondingly, a prospective observational study found that 32% COVID-19 survivors have cardiac damages 3 months after the onset of infection [36]. 89% of long COVID patients reported cardiac associated symptoms, where 53% reported chest pain, 68% palpitations and 31% new onset of POTS.

Long COVID can also affect the central nervous system (CNS). Chronic neuro-inflammation activates glial cells which lead to neurodegenerative disorders. SARS-CoV-2 can permeate through the blood-brain barrier (BBB), and subsequent damage of the BBB permeability will further drive neuro-inflammation in the brain parenchyma. Pathological hyperinflammatory and hypercoagulable conditions may increase the risk of thrombotic events. Furthermore, hyper-inflammation in the brainstem may lead to autonomic dysfunction. CNS dysfunction in the brain may contribute to long-term cognitive impairment. Multiple studies have proposed that CNS disturbance in response to neuro-inflammation could be responsible for the neuropsychiatric abnormalities, including chronic malaise, fatigue, sleeping disorder, ageusia and anosmia (loss of taste and smell), PTSD, conative impairment, and even stroke. In a UK retrospective cohort study on 23,6379 confirmed COVID-19 cases, one in three subjects reported neuropsychiatric symptoms 6 months after SARS-CoV-2 infection. Specifically, subjects with severe acute COVID-19 were at higher risk for neuropsychiatric morbidity. Imaging studies using structural magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging showed

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brain alterations among patients with cognitive impairment during subacute COVID-19 stage when compared to healthy controls. Combination of population and clinical data strongly suggest neurological involvement in long COVID.

Cardiovascular Complications

Patients who became sick with SARS-CoV-2 had heart problems after they got better, such as low blood pressure, a slow heart rate, and atrial fibrillation, and about 20% of COVID-19 patients who becamebetter reported chest pain up to 60 days later. The myocardial tissues, including the alveoli and the lungs, consist of an ACE2 receptor where the virus binds to the receptor and decreases expression of ACE2, which is a cardio-protective transmembrane protein widespread in many tissues such as the kidney, lungs, heart, and intestine. Moreover, following SARS-CoV-2 infection, many people are diagnosed with cardiac arrhythmias with an increased troponin level.

Several reports highlighted that pneumonia is a predominant symptom seen in SARS-CoV-2-affected patients, some of whom may require hospitalization. These patients have a high chance of having cardiovascular complications after recovery. Corticosteroids are infrequently suggested for COVID-19 patients with lung damage. However, in severe cases, corticosteroids were applied, which in turn affected the cardiovascular tissues. Reported cases also highlighted those patients with no history of cardiac problems who developed malignant arrhythmias and acute respiratory failure, leading to death. Moreover, the increased troponin level also resulted in the cardiac arrest of the patients after recovery. Based on the cases reported in previous outbreaks like SARS-CoV and MERS-CoV, 40% of recovered subjects have had persistent cardiovascular problems for a long time. The same scenario is expected in the case of COVID-19.

Respiratory Complications

SARS-CoV-2 mostly affects the lungs. The severe attack on the lungs develops critical manifestations such as respiratory failures and pneumonia, constituting a prime reason for COVID-19-associated mortality. Inflammation and pulmonary fibrosis are the two main effects of a viral lung infection. This inflammation affects the tiny air sacs called alveoli, which help in the diffusion of respiratory gases. Post-mortem analysis of several COVID patients has shown an extreme level of lung congestion, and the parenchymal cells present in the lungs are highly inflamed and appear to be bluish-red. The histopathological reports of lung tissue samples indicated the congestion of the small and large airways, including the pleural tissue and capillaries. These examinations also gave evidence of acute bronchopneumonia, emphysema, asthma, etc.. These severe complications have a high chance of being prevalent in the long run after the patient's recovery[17-19].

Most survivors of COVID-19 have pulmonary symptoms such as dyspnea, which have been reported in 42% to 66% of cases at 60 to 100 days of follow-up. When standard radiological imaging has been used to find respiratory problems, they have been described as having segmentation of the lungs and opacities that look like glass. The lung segmentation pattern shows how viral loads can damage the lungs and make them less able to hold air. In some patients (about 5%), the CTs (computed tomography scan) findings indicated lymphadenopathies, pleural effusions, and cavitations.

Gastrointestinal Complications

The fact that the ACE2 receptor is found in the GI (gastrointestinal) tract makes it easy for SARS-CoV-2 to take over. Patients who becamebetter had higher levels of SGPT (serum glutamic–pyruvic transaminase), SGOT (serum glutamic–oxaloacetic transaminase), bilirubin, and other enzymes that the liver needs to work well. The elevated levels had given clear evidence of the problem in the liver. Other than the liver, the other gastrointestinal complications include dysbiosis, visceral hypersensitivity, and enhanced intestinal permeability, which leads to inadequate absorption of bile acid together with problems related to some metabolic pathways. Moreover, evidence suggests that viral attacks may lead to functional gastrointestinal disorders or disorders in the gut–brain interaction, although this symptom does not persist for a very long time.

Neurological Complications

Spike protein–ACE2 receptor interaction leads to the dysfunction of cell signaling processing, which in turn affects the functioning of the olfactory and gustatory organs. This may lead to adverse neurological complications in the long run due to the entry of the virus into the brain via the nasal cavity. Stroke, encephalitis, and other cerebrovascular diseases are among the leading causes of human suffering. Post-

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Covid neurological problems thatare seen in a large number of patients include anosmia, headaches, and stroke in some cases. The pathway of the virus toward the brain leads to olfactory dysfunction (namely, anosmia). Normal neurological effects of this impairment fall into three groups: problems with the central nervous system, problems with the peripheral nervous system, and injuries to the bones and muscles. These manifestations together lead to headaches, dizziness, anosmia, vision problems, etc

Psychiatric Complications

The SARS-CoV-2 distresses the brain, which houses several neuronal circuits, just like the other two infectious members of the Coronavirideae family. A viral infection in the brain stem lowers the number of ACE2 receptors. This kills neurons and changes how several baroreceptors work. In the long run, post-traumatic stress disorder (PTSD) will be a common problem. This is not only due to the viral attack in the brain but also to this severe pandemic and a high mortality rate associated with many complications

Dermatological Complications

The urticarial lesions, maculopapular lesions, vesicular lesions, necrosis, and liver lesions that have been reported are caused by the interaction between the spike protein and the ACE2 receptor in the basal cells of the epidermis. Many of the patients even had oral ulcers and blisters. Another very common symptom observed in the case of children was rashes on the skin

enal Complications

Acute kidney injury (AKI), electrolyte disturbances, and renal replacement therapy (RRT) are some of the most common renal complications that have been associated with COVID-19 patients. A prominent cause of COVID-19-related death other than proteinuria and haematuria is AKI. Long-term renal complications in patients are also caused by AKI, potentially causing microalbuminuria and chronic kidney diseases

SARS-CoV-2 induces both direct and indirect pathology which contribute to multi-organ dysfunction. Hyperinflammation of kidney tissues may activate the complement system, contributing to focal segmental glomerulosclerosis and glomerular involution [30]. Acute kidney injury has been reported among discharged COVID-19 patients, and 35% of the recovered patients have reduced kidney function [43]. SARS-CoV-2 triggers pancreatitis during acute-COVID. Pancreatic damage as observed in long COVID may be consequences from a combination of direct viral attack and indirect effect of systemic inflammation. The major SARS-CoV-2 receptor ACE2 is an endocrine regulator in the renin-angiotensin-aldosterone system, while the other SARS-CoV-2 receptor TMPRSS2 is found in pancreatic β cells. The viral infection directly impairs ACE2 and TMPRSS2-expressing cells, causing dysfunctions in renin-angiotensin-aldosterone system and disrupts metabolic homeostasis in the long term. Furthermore, systemic inflammation and corticosteroids administration increase the risk of bone demineralization and dermatologic complications[20-21].

Treatments and management of long COVID patients

Medical experts are using their best efforts to manage patients with long COVID. Although several guidelines on long COVID management have been released, there remains a large practical gap and specific treatments are not reviewed. While empirical evidence still awaits to inform clinical practice, a comprehensive review of clinical strategies adopted by clinicians will be valuable in guiding appropriate patient rehabilitation [51]. It is important to optimize clinical outcomes by considering patient safety and enhancing sophisticated diagnosis and holistic assessment. Furthermore, novel therapeutics for treating organ specific dysfunction and long COVID related symptoms will guide treatment development. WHO have empathized research priorities in refining clinical characterization and developing therapeutics for long COVID. At the same time, medical professionals are exploring clinical approaches in identifying and managing long COVID.

Long COVID symptoms are presented heterogeneously, so patients need to be closely monitored. In order to develop effective treatment strategies, holistic assessment is necessary to consider pre-existing conditions and to identify specific symptoms. NICE outlines a set of evidence-based assessment and management approaches for treating patients with long COVID [52]. The NICE guideline recommends clinical investigation of long COVID as early as 4 weeks after initial acute symptoms. In addition, the National Institute of Health and Care Research (NIHR) also issued recommendations on the evaluation of long COVID symptoms and prioritizing care for certain populations.

In general, current clinical practice adopted a symptom-based approach in managing long COVID. Comprehensive assessment through medical history and

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examination is essential. It is recommended to obtain a complete assessment including full blood count, renal function test, C-reactive protein, liver function test, thyroid function, hemoglobin A1c (HbA1c), vitamin D, magnesium, B12, folate and ferritin levels. The International Consensus Conference in Critical Care recommends adopting screening tests for prediction and identification of physical and mental impairment. A robust clinical care also requires additional assessments for appropriate referrals to specialists. Importantly, while long COVID is diagnosed, other non-COVID-19 related diagnosis should also be considered unless they could be excluded. Appropriate treatments are provided according to clinical symptoms. For patients presenting with cardiopulmonary symptoms, chest imaging, electrocardiography and pulmonary function tests should be considered. Oxygen supplementation is commonly provided for patients with dyspnea and during pulmonary rehabilitation. In particular, corticosteroid treatments have been showed to resolve pneumonia and improve clinical functions. Sufficient patient support and rapport building are essential for disease recovery.

Mast cell activation syndrome (MCAS) and anti-histamine treatment

Previous findings have suggested the prevalence of mast cells activation syndrome in long COVID patients. It is suggested that immune disturbance from SARS-CoV-2 infection may lead to aberrant mast cell activation and further initiate cascades of inflammatory responses contributing to allergic flare-up. Histamine antagonists have been used to relieve long COVID associated symptoms . However, the interaction of antihistamines with viral-altered ACE2 pathways remains to be elucidated. One concern is that antihistamines can be easily assessed over the counter and abusive usage may lead to problems. Misuse of antihistamines will cause abnormal levels of circulating dopamine and may be associated with dementia in the long-term. Future studies and clinical trials are required to investigate antihistamines as therapeutic treatment for long COVID.

Dietary supplements

In long COVID, chronic inflammation provokes multi-organ damage and exacerbates pre-existing conditions. Dietary supplements, such as vitamins and minerals, contain anti-inflammatory and anti-oxidative components, so they have become potential treatments for long COVID. A pilot study demonstrates that multivitamin supplements improve clinical symptoms among long COVID patients. In addition, a commercial plant extract supplement from *Panax ginseng* and *Eleutherococcus senticosus* effectively relieved post-COVID fatigue and improved health status in 201 long COVID patients.

Long COVID patients often have dysregulated lipid oxidation and lactate accumulation during physically active state, indicating compromised mitochondrial function. The mitochondrial dysfunction in long COVID shares similar symptoms as the ones observed in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Supplementation with Coenzyme Q10 (CoQ10) is found to reduce fatigue frequency and relieve oxidative stress among ME/CFS patients .

Clinical indicators for long COVID

In order to effectively treat long COVID, it is crucial to have accurate diagnosis. Early diagnosis is essential for effective management and improved prognosis. Several clinical indicators have been developed to guide the clinical diagnosis of long COVID.

Serum biochemistry

Acute COVID-19 infection disturbs the immune system response and predisposes a low-grade inflammation state which may continue over subacute phase. Systemic inflammatory markers were proposed as biomarkers for long COVID. For instance, D-dimer, c-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin and neutrophil count found to be associated with persistence symptoms of long-COVID. Cardiac, hepatic and renal abnormalities are also observed among patients with abnormal CRP, procalcitonin and neutrophil count levels [67]. Analysis of endothelial function in 30 patients with long COVID reported distance ET-1 and RHI profile in long COVID patients . In addition, neurodegenerative indicators including amyloid beta, neurofilament light, neurogranin, total tau, and p-T181-tau were elevated among long COVID patients when compared to healthy controls.

To this end, it would be very helpful for long COVID diagnosis if a set of biostable biomarkers are available independent of symptoms. A recent study found that the immunoglobin profile of IgM and IgG3 is linked with increasing risk for developing long COVID. In fact, IgM and IgG3 are secreted by B cells in response to interferon induction and IL-4 signaling. Impairment in

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interferon synthesis characterized by increased interleukin signaling may contribute to inefficient IgG isotype conversion, debilitating immunity regulation. As the pandemic evolves, research emerges toward a predictive model for post-acute sequelae of COVID-19.

Gut microbiota

Immunomodulatory functions of gut microbiome are well documented in various disease pathogenesis . SARS-CoV-2 RNA can be detected from fecal samples during acute stage, indicating gastrointestinal (GI) involvement in COVID-19 pathology. Increase in viral-induced cytokines may compromise intestinal integrity, facilitating the entry of bacteria and metabolites into circulation. Such dysbiosis triggers the innate immune responses, causing pulmonary dysfunction and secondary infections [77]. Furthermore, integrative multi-omics profiling reveals that subjects with GI complications exhibit unique T cell signature during COVID-19 recovery [20]. Current findings open opportunities for gut microbiota to be used as a therapeutical approach by priming inflammation responses. A prospective study of 106 subjects identified specific patterns of intestinal microbiome profile predicted long COVID symptoms. For examples, elevated levels of *Ruminococcus gnavus*, *Bacteroides vulgatus* and reduced levels of *Faecalibacterium prausnitzi* and butyrate-producing bacteria correlated with long COVID. Such intricate association may serve as a detection tool for the occurrence of long COVID.

Proactive Management of long COVID

Considering that more and more people will likely be infected by emerging SARS-CoV-2 variants, long COVID will continue to affect the society immensely in the foreseeable future. It is critical for people to take proactive actions to relieve its potential impacts. In doing so, we need to understand the risk factors of long COVID, control the risk factors and avoid questionable practices[22-25].

Risk factors of long COVID

Ever since long COVID was first reported, much attention has been paid to identifying its risk factors. The understanding of risk factors allows people to correlate long COVID with various determinants such as pre-existing conditions, age, medical treatments, genetics and lifestyle. The specific correlations will guide clinical diagnosis and management of long COVID. Symptoms in long COVID arise from multisystem damage, a holistic approach should be considered when identifying at-risk individuals at early phase of the disease.

Severity of Acute COVID infection

Long COVID was first reported in hospitalized patients requiring mechanical ventilation during acute stage, suggesting the symptoms at this stage correlates with the prevalence and severity of long COVID. It is reported that viral load during acute COVID correlates with the severity of long COVID manifestation [20]. Early viral clearance seems to be protective from long COVID responses. Low viral load or early viral clearance probably leads to lower grade inflammatory reactions during acute phase, which results in less damage to the host in long COVID. The COVID Symptom Study shows that symptom quantity during the initial infectious week is predictive of long COVID duration.

In the past three years, the continuous viral evolution leads to the emergence of numerous SARS-CoV-2 variants in global populations, which challenges the effectiveness of public health in diagnosis, vaccination, and treatments. Five variants of concern (VOC) have been widely reported, and they are Alpha, Beta, Gamma, Delta and Omicron variants. Because of their specific mutations in viral genome, different variants have various transmissibility and virulence, which affects both Acute COVID-19 and long COVID in patients. Currently, Omicron variant is the dominant variant with enhanced transmissibility since February 2022, replacing Delta variant that was most prominent in 2021. A recent study showed that Omicron variant caused lower risk in developing long COVID in comparison to Delta variant among infected patients [84]. The finding is probably associated with the fact that Omicron variant generally caused less severe symptoms than Delta variant at Acute stage. However, because of its high transmissibility, more people will likely be infected by the Omicron variant. In this sense, Omicron variant associated long COVID will remain a major challenge for people in foreseeable future.

Pre-existing conditions

Pre-existing conditions correlate with the severity at acute stage, and are risk factors for developing long COVID. In a recent study, a combined analysis of UK primary care electronic health records and 10 population-based longitudinal studies revealed multiple risk factors for long COVID, including age, female

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gender, poor general health, asthma, and being overweight or obese. In a prospective cohort study of 215 participants, long COVID developed in 94% of participants with a history of asthma bronchial, compared to 59% in those without . The complex interactions of asthma severity, underlying conditions, as well as corticosteroid administration should be considered when managing long COVID. In addition to asthma, other pre-existing conditions were also reported to be long COVID risk factors. Pre-existing type 2 diabetes increase the risk of long COVID, as chronic inflammation associated with insulin resistance leads to a more profound immune responses during acute SARS-CoV-2 infection and subsequent COVID sequala. Poor mental health is associated with 50% increased risk of developing long COVID and an increase in its relative severity [85, 86]. Interestingly, history of Epstein-Barr virus viremia might increase the risk for long COVID as suggested from single-cell sequencing of long COVID subjects. With ongoing research, additional medical conditions may be identified as risk factors for long COVID.

Age

Advanced age is a main risk factor for the severity of acute infection, as well as the risk of long COVID. The COVID Symptom Study identified advanced age as a risk factor for long COVID [7]. Approximately one in five COVID survivor of over 70 years of age reported having lasting symptoms [87]. In contrast, self-reporting data from the UK's Office for National Statistic suggested subjects aged from 35 to 69 have the highest prevalence in experiencing long COVID [31]. Discrepancy of such results warrants further research to elucidate underlying mechanisms and identify long COVID patterns in different age groups. Considering that older patients are more likely to have pre-existing conditions and develop more severe acute responses, the increased risk of long COVID with advanced age may be a secondary effect[26-29].

Biological sex and sex hormones

Clinical data from epidemiological studies have drawn the attention toward the sex-discrepancy in long COVID. In general, females under age 50 are five times more likely to develop long COVID symptoms post-discharge when comparing to male COVID-19 patients. Ovarian abnormality following HIV and Hepatitis B/C infections has been previously reported. The abundance of ACE2 in ovarian granulosa cells and the hormonal disruption from SARS-CoV-2 may both contribute to ovarian dysfunction [25]. Specifically, perimenopausal and menopausal women are more prone to long COVID. Virus-mediated ovarian hormone disturbance interferes with systematic homeostasis reflects the inflammatory disorder over disease course in anticipating long COVID. However, overlapping symptoms of long COVID and menopause-related conditions pose additional challenges in the diagnosis and management of long COVID in this population.

Paradoxically, male sex is a risk factor for acute infection, but fewer long COVID cases are reported in male patients. It is noticed that long COVID studies are largely derived from self-reported data. Selection and reporting biases may arise from such methodological limitations. It is possible that part of the sex-associated long COVID prevalence may be linked to sex-dependent self-reporting. Meanwhile, sex-dependent discrepancy in medical care already exist in pre-COVID-19 era, so more complicated social issues could also lead to the increased number of female long COVID patients.

Treatment

Vaccination

Considering the impact of long covid to individual's wellbeing and society, it is important to take preventive measures besides trying to avoid infection. In the past two years, various vaccines have been developed for SARS-CoV-2. Although vaccines do not prevent infection, they significantly suppress morbidity and fatality. Two recent studies compared the long covid symptoms between unvaccinated patients and vaccinated patients in Israel [93] and the UK [94]. Both demonstrated that vaccination is strongly associated with the decrease of long COVID related symptoms. In fact, one of the studies showed that vaccinated people are no more likely to report long COVID symptoms than individuals without prior viral infection. In Switzerland, about 40% of death in connection with SARS-CoV-2 infection had not received COVID-19 vaccination in contrast to ~ 10% of death shared by individuals who had received at least single dose of vaccination. These data suggest that vaccination is beneficial in controlling both acute and long COVID-19 symptoms.

The fifth wave of COVID-19 outbreak in Hong Kong has alarmed the COVID-19 vaccine hesitancy and associated factors in the community [96, 97]. Vaccination

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coverage in Hong Kong declined with age, with 49% of individuals aged above 60 reported receiving at least two doses of COVID-19 vaccine. The COVID-19-associated mortality was prevalent among unvaccinated individuals aged above 60 years. The increased risk of COVID-19 severity among older population groups suggested relative risk for long COVID. Data from Hong Kong highlighted the important to implement strategies to boost vaccine coverage, especially among older adults.

In addition to vaccines specific to SARS-CoV-2, people reported that other unrelated vaccine might also provide protective effects. A study on health care workers showed that recent influenza vaccination reduced the risk of SARS-CoV-2 infection and COVID-19 severity [99]. A retrospective study also showed that influenza vaccination significantly decreased the risks of sepsis, stroke and deep vein thrombosis associated with long COVID, and reduced the admission to Emergency Department and Intensive Care Unit weeks after initial infection [100]. Besides from the novel COVID vaccination, the bacillus Calmette-Guérin (BCG) vaccine against tuberculosis holds general protection from wide range of infectious diseases . In the era of COVID, the BCG vaccine has been proposed against SARS-CoV-2 severity where BCG vaccination is shown to have negatively associated with COVID-19 mortality. One study showed that BCG vaccine against COVID-19 was significant in young population, but was not as effective in older population . However, another study from South Africa reported no protective effect by BCG vaccination against COVID-19 infection, severity and related mortality [106]. Above contradictory reports may contain analytic complications such as confounding mortality with tuberculosis and differences in demographics and diagnosis, so more human and animal studies are necessary to reveal whether influenza and BCG vaccines could stimulate the basal immune defense against SARS-CoV-2. In the absence of solid evidence, influenza and BCG vaccines are not recommended as a preventative vaccination for COVID-19.

Anti-inflammation treatment

Immunological aberrations owning to molecular mimicry induce autoantibody production which stimulates T cells and leads to tissue damage during acute COVID-19 infection . Therefore, combating inflammation responses is critical in managing viral manifestation as well as clinical sequelae of SARS-CoV2. Dexamethasone is commonly used to treat inflammation in acute COVID-19 patients. Dexamethasone-treated COVID-19 patients were less likely to experience long COVID symptoms at 8-month follow-up in an observational study [111]. This study suggests that disease treatment approach for acute COVID could have profound impact on patients' wellbeing in the long run.

Nutritional control and lifestyle modifications

Nutritional management plays an important role in the management of chronic illness, and appropriate nutrition may mitigate the manifestations of viral infections . Moreover, disparities in SARS-CoV-2 incidences across population indicate the plausibility of nutrition-related epigenetic variations among different populations.

Multiple observational studies and clinical trials have established the beneficial effect of vitamin D supplementation in preventing respiratory infections . For instance, numerous ongoing clinical trials are evaluating the clinical outcomes of vitamin D supplementation in the context of COVID. generally, vitamin D is derived primarily from UVB radiation exposure and dietary intake . Both UV-synthesized and ingested vitamin D then undergo two hydroxylation reactions to become activated as calcitriol[30-31]. Activated vitamin D is involved in multiple immune functions, including the maintenance of barriers, antigen presentation, innate immunity and adaptive responses. Furthermore, the regulatory roles of vitamin D in the renin-angiotensin-aldosterone system (RAAS) may contribute to its therapeutic potential in mitigating SARS-CoV-2 pathogenesis. Despite the association between vitamin D deficiency and SARS-CoV-2 infection, evidence to support vitamin D supplementation for long COVID management is still lacking. Although recent study did not find an association between vitamin D levels and persistent long COVID symptoms, vitamin D deficiency is known to be associated with fatigue and muscle weakness. Additional research is warranted to explore the relationship between vitamin D and the pathology of long COVID. Optimal vitamin D intake from sunlight exposure and vitamin D rich food (fish, mushroom, and vitamin d-fortified foods) may have proactive effects in preventing COVID-19 infection and relative long COVID risk.

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Conclusion

The study concludes that SARS-CoV-2 has been evolving quickly in the past two years, and multiple variants have gained increased abilities to infect patients or evade the protection by vaccination. Human species will likely co-exist with the virus for many years to come, so long COVID will remain a global challenge to health care system and economy. In order to effectively deal with long COVID, it is important to raise public awareness of its risk factors and take proper management options. With increasing knowledge of COVID-19, the society will be able to protect people's interests if everyone acts together. Long COVID, also called post-acute sequelae of SARS-CoV-2 infection (PASC), is a condition in which COVID-19 symptoms last for weeks or months after the initial infection has gone away. Most people becomebetter from COVID-19 within a few weeks, but some keep having a variety of symptoms that can have a big impact on their quality of life. It is unclear what causes long COVID, but it is thought to be related to the immune system's response to the virus. Some experts believe that the virus may trigger an autoimmune response in some people, which can lead to ongoing symptoms. Long COVID can affect people of all ages, including those who had mild or even asymptomatic cases of COVID-19. It is important to note that the condition is not well understood, and research is ongoing to better understand the causes and potential treatments. SARS-CoV-2 outbreak can be considered a unique mental health disaster. Most studies have reported psychological and neuropsychological problems (anxiety and depression, PTSD, sleep problems, and cognitive problems) post-COVID-19, even in people without previously diagnosed mental health problems. PTSD is the most prevalent long-term post-COVID psychiatric condition, followed by depression and anxiety disorders.

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