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Long COVID symptoms: Basic aspects of cardio-pulmonary and neurological pathways!

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Abstract

Long COVID is more prevalent chronic health care issue in post COVID care settings. We are in great piece of relief due to nearly end of this deadly pandemic which has caused significant change in routine of entire globe. Long COVID is an unpredicted sequel of COVID-19 disease documented nearly in half cases globally. Long COVID is multisystem syndrome with nonspecific symptoms and organic signs of unidentified pathology occurs after COVID-19 disease. Long COVID symptoms has been documented in 'selected' cases irrespective of disease severity or hospitalization and possible link remains unknown. Long COVID symptoms has significant impact on quality of life in those cases suffered from disease in recent past and lingering to almost two years since infection. Importantly, not all cases of COVID-19 were shown long COVID symptoms. Most common long COVID symptoms as joint pain, fatigability, chest discomfort, shortness of breath, hair loss, chest pain, weight gain, anxiety/depression & memory impairment. Pathophysiology resulting into long COVID manifestations is still not completely validated. Researchers have reported 'immune dysregulation', 'autoimmunity', 'antigenic mimicry' & 'coagulation abnormalities' are probable pathophysiological mechanism for long COVID. Some of the long COVID effects shown complete reversibility including post COVID lung fibrosis. Reboot system to restore immune dysregulation and recovery in long COVID is real concern. Long COVID symptoms cases are more health conscious and usually follows pattern of doctor shopping due to underestimation by family physicians either due to lack of suspicion or lack of knowledge regarding treatment protocol. Still, we are not having right answer for exact duration of long COVID symptoms and when it will show complete reversibility. Further, it needs 'birds eye vision' to pick up and manage cases with long COVID manifestations during routine care in rehabilitation unit.

Keywords: Long COVID; Joint pain; Fatigability; Immune dysregulation; Autoimmunity; Antigenic mimicry; Coagulation abnormalities; COVID-19

1. Introduction

COVID-19 is caused by the infection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a singled-stranded RNA coronavirus. Coronavirus disease 2019 (COVID-19) has escalated into an unprecedented global pandemic since the first case was identified in December 2019 [1]. Though a majority of patients recovered from COVID-19 infections, over 70%-of-survivors were reported to have impairments in one or more organs 4 months after initial symptoms [2]. They are termed "long haulers" [3], or patients living with "Chronic COVID syndrome", "post-COVID-19 syndrome", or "postacute-COVID19 [4,5]. Extensive symptoms have been reported by convalescent patients, such as chronic cough, chest tightness, shortness of breath, cognitive dysfunction, and extreme fatigue, in Long COVID-19 Syndrome [6]. Long COVID-19 Syndrome is an umbrella term, including post-acute COVID-19 and post-COVID-19 syndrome, depending on the duration after the acute onset of symptoms (Figure 1) [7].

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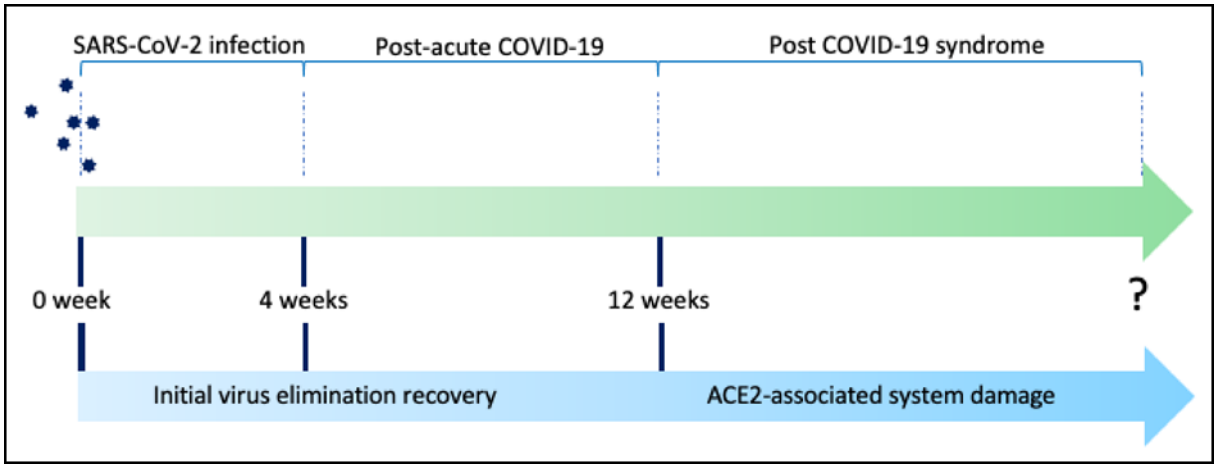

Figure 1 The timeline of Post-acute COVID-19 syndrome is defined as 4 to 12 weeks between initial confirmation of SARS-CoV-2 infection, while Post-COVID-19 syndrome is defined as 12 weeks after initial infection. The underlying progression/persistence of symptoms is associated with initial virus elimination recovery and angiotensin-converting enzyme 2 (ACE2)-associated system damage

Postacute-COVID-19 is defined as ongoing symptomatic COVID-19 for people who still have symptoms 4 and 12 weeks after the onset of acute symptoms, while post-COVID-19-syndrome is for people who still have symptoms for more than 12 weeks after onset of acute symptoms according to the UK NICE guidelines [6]. In a systematic review and meta-analysis looking into the long-term effect of COVID-19, the five most common symptoms are fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%) [8,9]. These symptoms may take months to resolve, even among non-hospitalized persons with mild illness course in the acute phase [10,11].

2. Pathophysiological mechanisms for Long COVID

The exact mechanism behind the persistence of symptoms has to be identified. Reason for the persistence of symptoms can be the sequelae of organ damage, varying extent of injury (organ damage) and varying time required for the recovery of each organ system, persistence of chronic inflammation (convalescent phase) or immune response/auto antibody generation, rare persistence of virus in the body, nonspecific effect of hospitalization, sequelae of critical illness, post-intensive care syndrome, complications related to corona infection or complications related to co morbidities or adverse effects of medications used [12,13].

SARS-CoV-2 uses the angiotensin-converting-enzyme 2 (ACE2) receptor to enter the cell through binding with spike-like protein (S-protein) [14,15], though some other receptors may also be involved. ACE2, therefore, plays a vital role in the pathogenesis of COVID-19. ACE2 is widely expressed in different body tissues, including the lung, heart, liver, kidney, and gastrointestinal system [16]. Thus, multi-organ injuries are observed in COVID-19, such as acute respiratory distress syndrome, acute myocardial injury, acute kidney injury, and acute liver injury. Survivors of severe COVID-19 are also found to be with multi-organ impairments after discharge [17].

2.1. Dysregulated inflammation in ongoing COVID and its impact on long COVID

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Pathophysiological mechanism is immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues.[18] Severity of illness increases with more lung parenchymal involvement as documented with chest imaging in proportion with inflammatory markers such as IL-6, CRP, Ferritin and LDH [19-22]. Authors have documented persistent smouldering infection as underlying mechanism for long COVID [23]. Second hypothesis is that mast cell activation syndrome could possibly contribute to long COVID symptomatology [24-25]. The third hypothesis put forth that sustained dysregulated immune system activation with subsequent chronic low-grade inflammation could lead to pathological consequences like autoimmunity leading to organ dysfunction [26-27] or antigenic cross reactivity or mimicry [28-31]. Authors have documented long-lasting functional alterations of T-cells, with persistence of cytotoxic profile with decrease in dendritic cells revealed 7 months post-infection [32-33]. Residual excessive inflammation after infection & auto-antibodies against immunomodulatory proteins or against tissues are other proposed mechanism for long COVID [34-35]. Other possible hypothesis is persistence of SARS-CoV-2 in the lower gastro-intestinal tract was revealed in asymptomatic subjects

several months after COVID-19, suggesting that residual viral proteins within tissues could possibly be the basis for a persisting immune reaction [36].

2.2. Coagulation abnormalities in ongoing COVID and its impact on long COVID

Acute COVID-19 infection is also characterized by dysregulated, circulating inflammatory biomarkers, hyperactivated platelets, damaged erythrocytes and substantial deposition of microclots in the lungs [37-39]. In those discharged with elevated biomarkers, 30.1% and 9.5% had persistently elevated D-dimer and C reactive protein, respectively. 38% of chest radiographs remained abnormal with 9% deteriorating [40]. In the largest global study to-date on this issue, a survey of 3,762 Long COVID/PASC patients, from 56 countries found nearly half still could not work full-time 6 months post-infection, due mainly to fatigue, post-exertional malaise, and cognitive dysfunction [41]. Data is available regarding vascular changes and thrombotic microangiopathy, diffuse intravascular coagulation and large-vessel thrombosis are major reasons for a poor COVID-19 prognosis [42]. These comorbidities are linked to multisystem organ failure, as well as pulmonary vascular endothelialitis. The presence of endotheliopathy in particular, is likely to be associated with critical illness and death [43]. It is also suggested that endothelial dysfunction contributes to COVID-19 associated vascular inflammation, COVID-19 associated coagulopathy, and pulmonary fibrinous microthrombi in the alveolar capillaries. In some instances, patients present with a significant elevation in D-dimer/fibrinogen degradation products. D-dimer and fibrinogen degradation products may indicate the failing attempt of the fibrinolytic system to remove fibrin and necrotic tissue from the lung parenchyma (and also from the circulation), but being consumed or overwhelmed in the process [44-45].

2.3. Symptomatology in long COVID and proposed pathways:

Long term symptoms following COVID-19 have been observed across the spectrum of disease severity. The current disparities between long COVID epidemiology reporting are owing to many reasons, including the length of follow-up period, population assessed, accuracy of self-reporting, and symptoms examined. Numerous symptoms of long COVID have been reported and attributed to various organs, an overview of which can be seen in fig 2. [46]

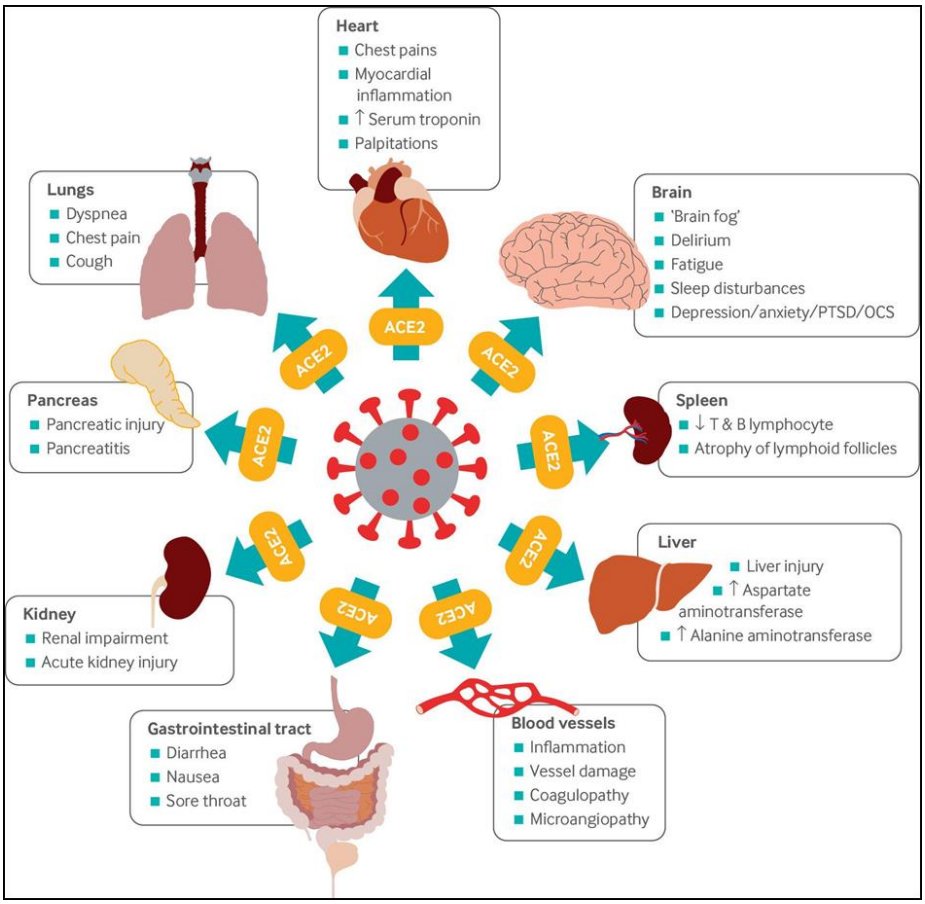

Figure 2 Multi-organ complications of COVID-19 and long COVID. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor

2.4. Long COVID symptom fatigue & possible mechanisms

Fatigue is more profound than being overtired; it is unrelenting exhaustion and a constant state of weariness that reduces a person's energy, motivation, and concentration. Following the SARS outbreak, up to 60% of patients reported ongoing fatigue at 12 months following recovery from the acute illness [47]. Fatigue is a common persisting symptom regardless of severity of the acute stage of COVID-19. One cross-sectional study found that 92.9% and 93.5% of hospitalized and non-hospitalized COVID-19 patients, respectively, reported ongoing fatigue at 79 days following onset of illness [48]. Many other cross-sectional and cohort studies report that chronic fatigue is the most frequently reported symptom following recovery from acute COVID-19 [49-51].

Fatigue is more profound than being overtired; it is unrelenting exhaustion and a constant state of weariness that reduces a person's energy, motivation, and concentration. Chronic fatigue following viral infection may be the result of miscommunication in the inflammatory response pathways [52]; however, a cross-sectional analytical study found no association between pro-inflammatory markers and long-term fatigue in COVID-19 patients with persisting fatigue [49]. It is likely that a range of central, peripheral, and psychological factors play a role in the development of post-COVID-19 fatigue. A narrative review explains that congestion of the glymphatic system and the subsequent toxic build-up within the central nervous system (CNS), caused by an increased resistance to cerebrospinal fluid drainage through the cribriform plate as a result of olfactory neuron damage, may contribute to post-COVID-19 fatigue [53].

Hypometabolism in the frontal lobe and cerebellum has also been implicated in COVID-19 patients with fatigue and is likely caused by systemic inflammation and cell mediated immune mechanisms, rather than direct viral neuro-invasion [54,55]. It is unknown whether this finding continues into long COVID.

Negative psychological and social factors associated with the COVID-19 pandemic have also been linked to chronic fatigue [56,57]. Lastly, peripheral factors such as direct SARS-CoV-2 infection of skeletal muscle, resulting in damage, weakness, and inflammation to muscle fibers and neuromuscular junctions may contribute to fatigue [58-61]. Overall, it is probable that several factors and mechanisms play a role in the development of post-COVID-19 fatigue.

Post-COVID-19 fatigue has been compared with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with many overlaps between the two [62]. Symptoms common to both ME/CFS and long COVID include fatigue, neurological/pain, neurocognitive/psychiatric, neuroendocrine, autonomic, and immune symptoms, with both ME/CFS and long COVID patients having long symptom durations, reduced daily activity, and post-exertional malaise [62]. ME/CFS remains enigmatic, therefore, research into long COVID may assist in developing understanding of ME/CFS and vice versa.

2.5. Long COVID symptom dyspnea & possible mechanisms

Breathlessness is common in people with long COVID. Abnormalities in diffusion capacity for carbon monoxide, total lung capacity, forced expiratory volume in the first second, forced vital capacity, and small airway function, have been seen in hospitalized COVID-19 patients at time of discharge, approximately one month following onset of symptoms, showing that lung function in people who have had COVID-19 may take time to recover [63]. Several studies have found that dyspnea is a common manifestation following COVID-19 infection, [40,50] and one study reported that 43.4% of 143 patients assessed were still experiencing dyspnea at 60 days after COVID-19 onset [51].

As COVID-19 is principally a respiratory illness, acute illness can cause substantial damage to the lungs and respiratory tract via SARS-CoV-2 replication inside endothelial cells, resulting in endothelial damage and an intense immune and inflammatory reaction [64,65]. Those who overcome the acute infection may develop long term lung abnormalities, leading to dyspnea [66]; however, most individuals who develop long-term breathing difficulties post-COVID-19 have no signs of permanent or long-lasting lung damage [67]. It is likely that only those at high risk of developing breathing difficulties, including older people, those who endure acute respiratory distress syndrome, those who have extended hospital stays, and those with pre-existing lung abnormalities, are prone to develop fibrotic-like changes to lung tissue [68]. The fibrotic state observed in some patients with ongoing dyspnea may be provoked by cytokines such as interleukin-6, which is raised in COVID-19 [69] and is involved in the formation of pulmonary fibrosis [70]. Pulmonary vascular thromboembolisms have been observed in patients with COVID-19 [71] and may have detrimental consequences in patients with long COVID.

2.6. Long COVID symptom with cardiovascular abnormalities fatigue & possible mechanisms

Cardiac injury and elevated cardiac troponin levels are associated with a significantly increased risk of mortality in patients admitted to hospital with acute COVID-19 infection [72,73]. Persisting cardiovascular abnormalities may be

burdensome for people with long COVID. A cohort study showed cardiac involvement, ongoing myocardial inflammation, and elevated serum troponin levels in many people with COVID-19 at 71 days following diagnosis, [51] while a large case series showed that chest pain, possibly owing to myocarditis, was a common manifestation in patients 60.3 days following onset of COVID-19 symptoms, with 21.7% of the 143 patient assessed reporting chest pain.[74] Those considered at low risk of severe COVID-19, such as young, competitive athletes, have also been found to have residual myocarditis long after recovery from COVID-19 [74]. In addition to cardiac complaints, studies have highlighted an emerging trend in the development of new onset postural orthostatic tachycardia syndrome (POTS) in individuals post-COVID-19 infection, because of autonomic dysfunction [75-79].

ACE2 receptors are highly expressed in the heart, [80] providing a direct route of infection for SARS-CoV-2. Studies have shown that sarcomere disruption and fragmentation, enucleation, transcriptional changes, and an intense local immune response occurs in cardiomyocytes infected by SARS-CoV-2 [81,82]. Pathological responses to acute cardiac injury and viral myocarditis, such as endothelial damage and microthrombosis, can lead to the development of coagulopathy, [83] while chronic hypoxia and an increase in pulmonary arterial pressure and ventricular strain may further precipitate the incidence of cardiac injury in people who have had COVID-19 [84]. Furthermore, sustained immune activation can lead to fibrotic changes [85] and displacement of desmosomal proteins, [86] which could be arrhythmogenic. Viral infection has previously been shown to precede POTS [87] and, with the ACE2 receptor expressed on neurons, viral infection by SARS-CoV-2 may have direct negative consequences on the autonomic nervous system [88]. A complex combination of infection, an autonomic nervous system induced pro-inflammatory response, and a level of autoimmunity may all contribute to the establishment of autonomic dysfunction and POTS [79].

2.7. Long COVID symptom & possible mechanisms for Cognition and mental health

Studies have explored cognitive function and deficits in patients with COVID-19 and suggest that the virus can cause septic encephalopathy, non-immunological effects such as hypotension, hypoxia, and vascular thrombosis, and immunological effects such as adaptive autoimmunity, microglial activation, and a maladaptive cytokine profile [89]. Additionally, patients admitted to hospital with COVID-19 have presented with a range of complaints including encephalopathy, cognitive impairment, cerebrovascular events/disease, seizures, hypoxic brain injuries, corticospinal tract signs, dysexecutive syndrome, an altered mental status, and psychiatric conditions [90-92]. These findings reveal that neurological symptoms associated with COVID-19 are common, diverse, and could pose substantial problems for rehabilitation and ongoing care following recovery from COVID-19. It is unknown who is most affected by cognitive complaints induced by COVID-19 and how long they persist; however, patient experiences and published summaries of long COVID have described “brain fog” to be a common and debilitating symptom [93-95].

Critical illness, severe acute respiratory syndrome, and long-term ventilator support are known to have detrimental effects on long term cognition. Before the COVID-19 pandemic, a retrospective study of 1040 ICU treated patients who had respiratory failure, shock, or both during hospital stays, found that 71% had delirium which lasted around four months following discharge [96]. A similar study found that, at 3 months post-discharge, 40% of ICU treated patients had cognition scores like those of patients with moderate traumatic brain injury, while 26% had scores similar to patients with mild Alzheimer’s disease. Delirium was also widely reported, with a longer duration of delirium associated with worse cognition [97]. With many COVID-19 patients requiring ICU admission and mechanical ventilation, long term cognitive impairment and delirium are likely to pose considerable problems.

Stroke and headache are prevalent in those recovered from acute COVID-19, with the ONS estimating the 5-week prevalence of headache at 10.1% of all COVID-19 survivors [98-101]. Exaggerated levels of systemic inflammation, observed in some patients as a “cytokine storm,” in addition to activation glial cells, poses a substantial risk to the brain and increases the likelihood of neurological manifestations including encephalitis and stroke [102,103] Hypercoagulability [104,105] and cardio-embolisms, formed because of virus related cardiac injury, [106] are manifestations that could result in increased incidences of stroke following COVID-19 infection. COVID-19 has also been associated with an increased risk of developing neurological conditions including Guillain-Barré syndrome, [107] and neurodegenerative conditions such as Alzheimer’s disease [108].

The pandemic has had a negative effect on mental health, with people who have had COVID-19 exhibiting long term psychiatric symptoms including post-traumatic stress disorder (PTSD), depression, anxiety, and obsessive-compulsive symptoms following recovery from the acute infection [109-112]. Quarantine, isolation, and social distancing also have damaging effects on mental health and cognition. A rapid review article states that the longer a person is confined to quarantine, the poorer the outcomes for their mental health, [57] while periods of isolation and the inability to work can cause anxiety, loneliness, and financial concerns, and living through a global health crisis can lead to avoidance behaviors and behavioral changes [113]. The mental health of the older population is greatly affected by social

distancing and similar measures. By assessing the associations between loneliness, physical activity, and mental health both before and during the pandemic, one study found that negative changes of these factors were not solely owing to longitudinal situations before 2020, therefore the pandemic exerted extra unfavorable effects on loneliness, physical activity, and mental health [114]. People living in care homes, including people with dementia, are vulnerable to COVID-19 and to other impacts of the pandemic. Those with dementia in care homes have been observed to become more depressed, anxious, agitated, and lonely [115]. Protracted social isolation has resulted in exacerbation of neuropsychiatric and behavioral disturbances, including apathy, anxiety, agitation, boredom, and confusion in dementia patients living in care homes, to a greater degree than for care home residents without dementia [116,117].

Sleeplessness is also commonly reported following recovery from COVID-19, with many studies finding poor sleep quality and sleep disturbances to be frequent following recovery from acute illness [40,118-120]. Furthermore, a retrospective study of medical records of COVID-19 patients treated in Seoul, South Korea, found that after prescriptions to treat fever, cough, and rhinorrhea, medications for sleep problems were the next most prescribed treatments [121]. Knowledge of the COVID-19 death toll also has a negative impact on quality of sleep, stress, anxiety, and other negative emotions, [122] and sleep problems have been shown to be associated with COVID-19 related loneliness [123]. This leads us to question whether post-COVID-19 sleep disturbances are a result of COVID-19 infection, the negative effects of the pandemic, or a combination of both. Mitochondrial swellings secondary to hypoxic damage are being observed in Long COVID-19 patients [124]. Neurons with high metabolic demand of oxygen, thus, become dysfunctional, leading to impairments of cognitive functions. This has been similarly observed in other pandemics [125]. The hypometabolism in parahippocampal gyrus, thalamus, and some white matter may be a secondary result of hypoxic damage to these areas, leading to memory loss and cognitive dysfunctions [126].

Coronaviruses including SARS-CoV-2 can infect the central nervous system (CNS) via hematogenous or neuronal retrograde neuro-invasive routes [127]. The entry mechanism and subsequent CNS infection may explain the high incidence of neuro-inflammation seen in patients with COVID-19, and may result in damaging long term effects, with associations of viral infections and chronic neuro-inflammation with neurodegenerative and psychiatric disorders already elucidated [127,128]. SARS-CoV-2 may also affect the permeability of the blood-brain barrier, which would enable peripheral cytokines and other blood derived substances to enter the CNS and further drive neuro-inflammation [129] Thrombo-inflammatory pathways may be the cause of the increased prevalence of stroke in COVID-19, [130] while “brain fog” may evolve from PTSD or deconditioning following critical illness and invasive treatment [131]. Evidence suggests that a direct viral encephalitis, systemic inflammation, peripheral organ dysfunction, and cerebrovascular changes may contribute to the development of long term sequalae following COVID-19 [132].

2.8. Long COVID symptom & possible mechanisms for Olfactory and gustatory dysfunction

Abnormalities of smell and taste have been reported to persist following recovery from COVID-19. The ONS estimated the 5-week prevalence of loss of smell and loss of taste as 7.9% and 8.2% of all people who have had COVID-19, respectively.[133] Other studies have found varying prevalence of olfactory and gustatory dysfunction, ranging from 11% to 45.1% of cohorts of patients who have recovered from acute COVID-19 [134-136].

Non-neuronal expression of the ACE2 receptor may enable entry of the SARS-CoV-2 virus into olfactory support cells, stem cells, and perivascular cells. This local infection could cause an inflammatory response which subsequently reduces the function of olfactory sensory neurons. Additionally, by damaging the support cells responsible for local water and ionic balance, SARS-CoV-2 may indirectly reduce signaling from sensory neurons to the brain,[137] resulting in a loss of sense of smell.

ACE2 receptors are also expressed on the mucous membrane of the oral cavity, particularly on the tongue, [138] therefore SARS-CoV-2 has a direct route of entry into oral tissue, which may result in cellular injury and dysfunction. Moreover, SARS-CoV-2 may bind to sialic acid receptors, [139] causing an increase in gustatory threshold and resulting in degradation of gustatory particles before they can be detected [140]. Another possible mechanism of gustatory dysfunction in COVID-19 and long COVID concerns the functional link between taste and smell, whereby gustatory perception is reduced because of antecedent olfactory sensory dysfunction [141].

Lastly, we recommend to assess inflammatory markers assessment in all cases suspected with any respiratory and systemic symptoms during follow up in post covid care setting especially those having any systemic long covid manifestations [142-154]. These markers have played significant role in assessment of cases form entry point to follow up and sequential change will guide to predict early chances of long covid symptoms and post covid sequel in selected symptomatic cases of recovered COVID-19 cases [152-160].

3. Conclusion

Long COVID in known complication of COVID-19 disease irrespective of severity and hospitalization. Long COVID can be predicted during hospital discharge in selected cases with inflammatory and coagulation pattern abnormalities. Long COVID should be actively evaluated in those cases with aggressive interventions in indoor units and comorbidities. Importantly long COVID pulmonary manifestation as lung fibrosis is reversible and now considered as post COVID sequelae.

Long COVID is underestimated, improperly evaluated and half-heartedly treated during follow-up due to lack of suspicion especially in geriatric cases. All treated cases need prompt evaluation, more awareness regarding its manifestations and its impact on quality of life is must to have successful treatment outcome. Vaccination will prevent long COVID in majority and decrease severity of illness in survivors. Still, we are not having right answer for exact duration of long COVID symptoms and when it will show complete reversibility. Further, it needs 'birds eye vision' to pick up and manage cases with long COVID manifestations during routine care in rehabilitation unit.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest.

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