

## LONG TERM COMPLICATIONS OF COVID-19

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### Abstract

SARS-CoV-2 pandemic started in December 2019. Some countries have seen second and even third wave of infection. Unlike in the beginning of the pandemic, the management of the infection has improved over the period resulting in less morbidity and mortality. This is because of improved knowledge of the disease due to several studies that are conducted during last one year. However, of late what are worrying are the long-term complications of the disease. The most common being the post covid fatigue, which lasts more than six months in some patients resulting in not able to carry out routine work as well as earning livelihood. Other common complications are pulmonary, cardiac, renal and neurological. The exact mechanisms of these complications are not known. The real problem is that there is no definite treatment for these complications. Resting, relaxing and reassurance are the treatment practiced now apart from organ/system specific management. Since the pandemic is recent one we may have wait for some more time to get more information of long-term sequelae of COVID19.

### Introduction

Covid-19 pandemic that has practically paralyzed the whole world in terms of economy, education and people movement has seen second and third waves in different regions of the globe. As of December 2, 2020, total number of COVID-19 cases are 64,526,022, total number of recovered cases are 44,736,632 recovered and 1,493,487 cases succumbed to the disease. There are 18,295,903 active cases and 44,736,632 cases recovered from COVID-19[1]. Studies have shown that people with blood group 'O' are less likely to get COVID-19 infection compared to A, B and AB groups and even if they get it is of less severity. Further individuals with Rh-ve blood group are more protective against COVID-19 compared to Rh+ve ones [2]. Some of the countries even enforced the lock down again due to second or third wave disrupting the life of the people. Due to improved knowledge of the disease and treatment protocol during the last eight months, the morality is at check though not controlled. Many pharma giants have developed the vaccines and have completed the phase III trials and waiting to hit the market at any time from now. Many more vaccines developers are actively involved in its production and are at various phases of clinical trials. Maximum individuals with SARS-CoV-2 experience mild to moderate symptoms. About 10-15% of patients advance to severe course disease, and nearly five percent develop seriously ill. Classically, individual get well from SARS-CoV-2 after two to six weeks. Few of

them may have linger or recur of symptoms for weeks or months succeeding initial improvement. This is seen not only in severe cases but also in also mild cases. They are non-infectious during this period. Few patients progress to medical problems that may result in lasting adverse health outcomes [3]. In a multistate study conducted in United States of America, patients complained of exhaustion, cough, breathlessness, ageusia or anosmia, headache and myalgia. Gastrointestinal symptoms such as nausea, diarrhea and abdominal pain are also reported [4].

In an app tracker study involving 4 million people in Bratain, the symptoms reported are fatigue(52%), shortness of breath(42%), joint pain(26%), chest pain(22%), cough(16%), loos of smell(15%), Sicca syndrome(14%), runny nose(13%), red eyes(10%), loss of taste(10%), headache(8%), sputum production(7%), lack of appetite(7%), sore throat(6%), vertigo(5%), muscle pain(5%) and diarrhea(3%)[5].

Of late, two issues related to COVOD-19 infection gaining more importance. One is long-term complications of COVID-19 and the other one is reinfection in COVID-19 recovered patients. Former is affecting the quality of life and later results in more severe infection and increased mortality rate. This review addresses some salient update of the long-term complications of COVID-19, it incidence, presentations and outcome and treatment options available.

### Long-term complications of COVID-19

Usually in the SARS-CoV-2 infected individuals, recovery from the illness happens in two following the first symptoms. Some of the cases who had more severe disease patients take longer - up to 6 weeks- to recover – They are called “long-hauler” [6]. In an app tracker study involving 4 million people in United Kingdom, it is also reported that one or other symptoms persisted for 90 days in two percent of the cases [5]. Long COVID can be a combination of four different syndromes seen in an individual at the same time [7]. They are post-viral fatigue, post-intensive care syndrome, permanent organ damage and long-term COVID syndrome. Majority of these problems may be due to the inflammatory response to disease. Ventilated patients may not recover fully and they may develop pulmonary fibrosis resulting in poor oxygen exchange and breathlessness [7]. About forty percent of cases had renal damage needing dialysis. Most probably impaired oxygenation to kidney due to its inflammation and poor lung function resulted in renal damage. It is also observed that younger patients are most likely to recover from renal damage, but the residual effect may progress without symptoms until the kidneys are damaged [7]. It is also reported that some people who never knew that they had covid because they are symptomless actually may be suffering more than the patients who are hospitalized and ventilated. [7].

#### Symptoms suffered during long covid

Nearly 35% of symptomatic adults who had a positive test result for SARS-CoV-2 did not returned to their earlier condition of health when interviewed two to three weeks following testing. Out of those, patients with 18 to 34 years of age were in good health. One in five patients reported that certain symptoms were extended. Patients with hypertension, obesity, psychological health conditions etc. are at higher risk of prolonged symptoms [4].

In another study, about 10%-35% of people with mild COVID-19 went in to long COVID symptoms. Alopecia, mental disturbance and cognitive difficulties, continuing headache, lymphadenopathy, long-term anosmia and ageusia taste and respiratory problems [7].

A study of 143 people from Italy, one of the earliest affected countries, reported that 87% of people discharged from a Rome hospital were still experiencing at least one symptom 60 days after the onset on Covid19 and 55% had three or more symptoms including fatigue (53%), difficulty in breathing (43%), joint pain (27%), and chest pain (22%) with 40% saying it had reduced the quality of their life [8].

On 5th June 2020, NHS England published ‘After-care needs of inpatients recovering from COVID-19’. This estimated that up to that date, more than 95,000 patients had been admitted to hospitals across England with Covid19 and it assumed 45% would need ongoing support<sup>2</sup>. Some estimates suggest that up to 50% of people hospitalized would need formal rehabilitation services [9,10].

### Does earlier coronavirus infections had long-term health effects

Individuals who had severe acute respiratory syndrome (SARS) due to the coronavirus in the year 2003 showed continuing and significant diminishing of exercise capacity and health conditions in fighters of SARS over two years. The adverse impact was more in health care workers who had SARS [11].

Lam et al reported that 40% of people had chronic fatigue symptoms lasting for nearly 3.5 years after being diagnosed with SARS [12]. So, the long term complications seen with COVID-19 is similar to the one seen with SARS of 2003, but the progression of COVID-19 yet to be established since it is just one year since the pandemic started.

As mentioned previously there four syndromes that can develop following COVID-19 infection, namely 1. Permanent organ damage to the lungs and heart, 2. Post-intensive-care syndrome, 3. Post-viral fatigue syndrome and 4. Continuing Covid-19 symptoms [13].

#### 1. Permanent organ damage to the lungs and heart

##### a) Pulmonary complications

The long-term pulmonary problems of covid-19 infection yet to established in terms of extent and severity, but evolving data point out that many patients experience continuing respiratory symptoms months after primary illness [14]. NHS guidelines mentions clearly the aftercare needs of patients convalescing from covid-19. The potential respiratory problems include cough, lung fibrosis, bronchiectasis, and pulmonary vascular disease. The evidence for these possible sequelae is largely derived from acute manifestations of covid-19, along with extrapolations from SARS and data on ARDS (Acute respiratory distress syndrome) [15]. About thirty percent of people with SARS or Middle East respiratory syndrome had long lasting pulmonary anomalies after their acute illness [15]. Two prospective studies of healthcare professionals with nosocomial SARS infection in Beijing and Hong Kong for two and fifteen years, respectively, reported persisting pulmonary abnormalities [11,16]. The treatment for inflammation induced interstitial lung fibrosis is administration of anti-inflammatory drugs [17]. Steroids in high doses were administered regularly to these patients which explains the limited incidence of fibrosis seen [11,16]. The beneficial effect of steroids such as dexamethasone in severe covid-19 has recently been proved; however, treatment did not improve acute outcomes among patients with milder disease [18]. The long-term outcome of steroids in the treatment of covid-19 has not yet been assessed but indiscriminate use may result in substantial morbidity.

##### Happy hypoxia

Debate as to whether hypoxemic respiratory failure from COVID-19 is ARDS, another process similar to high-altitude pulmonary edema (HAPE), or some other novel

syndrome. An imbalance in Starling forces due to inflammatory damage of the alveolar epithelium and endothelium and increased capillary permeability, leading to fluid accumulation in both alveolar spaces and interstitium leading to ventilation–perfusion mismatch and hypoxemia. The HAPE is due to excessive hypoxemic pulmonary vasoconstriction, and not an inflammatory process [19,20,21].

### **b) Cardiac Complications**

In August 2020, a NICE rapid review reported that acute myocardial injury is the most commonly described cardiovascular complication in Covid19, occurring in 8–12% of all those discharged with heart failure and arrhythmias[22]. The cardiovascular complications in COVID-19 patients may be more in individuals with following risk factors. They are old age, preexisting lung, renal, cardiovascular disease, diabetes mellitus, systemic inflammatory conditions, coagulation abnormalities, multiorgan failure and prolonged immobility. The complications seen in these patients are myocardial injury and myocarditis, acute myocardial infarction, heart failure, cardiomyopathy, arrhythmias, cardiac arrest and venous thromboembolic events.

Patients with acute myocarditis may have erratic array of clinical severity and poses a definite diagnostic challenge. Common presentations are chest pain, dyspnea, dysrhythmia, and acute left ventricular dysfunction [23,24,25,26,27]

Abnormal serum troponin levels are seen in patients with myocarditis and myocardial injury. The ECG findings include non-specific ST segment-T wave abnormalities, T wave inversion, and PR segment and ST segment deviations (depression and elevation). Abnormal serum troponin in COVID-19 infected patients is an indication of adverse outcome, including mortality [28,29]. There are chances of atherosclerotic plaque disruption and acute myocardial infarction [AMI] in patients with severe inflammatory reaction[30]. Both severe inflammation and increased coagulation contributes to the increase in risk of AMI in COVID-19 patients [31]. The treatment of AMI in these cases is controversial. The treatment considered for ST elevation myocardial infarction (STEMI), COVID-19 with no right ventricular involvement is fibrinolysis, and percutaneous coronary intervention is the treatment of choice in lateral AMI without hemodynamic compromise [31].

Some COVID-19 infected patients may present primarily with AMI. Zhou et al reported that AMI may be present in twenty-three percent of patients in their initial presentation for COVID-19, nearly thirty-three percent may develop cardiomyopathy [26] and heart failure was present in twenty-four of cases and was associated with an increased risk of mortality [28]. About fifty percent patients with heart failure did not have a known history of hypertension or cardiovascular diseases [32]. This cardiac problem needs

to take in to account while administering the intravenous fluid to avoid overloading of the already decompensated heart. About seven percent of COVID-19 patients may present with palpitations [33].

The most common cardiac arrhythmias seen in COVID-19 patients is sinus tachycardia. The causes for sinus tachycardia are multiple, namely ischemia, hyperpyrexia, hypoxia, anxiety, etc)[34]. COVID-19 patients are also at an increased risk of ventricular extra systoles (VTE) [30,31]. The cause for VTE are systemic inflammation, altered coagulation, multiorgan failure, and serious illness [25]. Zhou et al reported that in patients with COVID-19 there is significant coagulation abnormalities and elevated D-dimer level [26]. Treatment with low molecular weight heparin has reduced the mortality in patients with severe COVID-19 infections or those patients with D-dimer more than six times the normal [35].

### **2. Post intensive care syndrome**

A common believe around the world is that once a patient is sent from the hospital and is tested negative the problem is over. However, the reality is different. People including the health care workers are not aware of a condition known as Post-Intensive Care Syndrome (PICS). PICS may be a community health calamity that public may come across when the pandemic slowdown a bit. Hence, it is most important to recognize this problem early and not to ignore it until it becomes a serious issue around the world. The common findings in PICS are decrease in physical ability, intellectual decline and disturbance in mental health condition that remain for prolonged time following discharge from the intensive care unit [36]. Nearly 20% of those admitted in intensive care unit require empathetic care [44]. About 50% of the patients admitted to intensive care units requiring ventilation may develop PICS and these patients have comorbidities like diabetes mellitus, high blood pressure, bronchial asthma, chronic obstructive lung disease [37].

Nearly forty-six patients at year one may exhibit neurocognitive deficits such as anxiety and depression and about 47 % of ICU survivors may develop similar deficits at two-year follow up [38]. The patients also complained of poor quality of life for one to two years of discharge from ICU [38]. This may result in their return to work, nearly 30% of them may have change their job, and a significant number may lose their job. [39]. It is reported that about thirty-three percent of post COVID-19 patients after their discharge from ICU are not able to drive vehicle resulting restriction on their movement and social responsibilities. COVID-19 pandemic just completed its first anniversary and the statistics we have now is unable to recognize the impending disaster [40]. Hence it important to tackle this problem by developing an integrated rehabilitation response. A health care team comprising of physical therapists, occupational therapists, psychologists, nutritionist and physical medicine and physiatrists can work jointly to develop policies to manage the problems arising

from ICU admission [41]. Good food and exercise designed to increase physical strength results in increased working ability and this should start early after discharge. Jones et al has reported that patients recovering from ICU at hospital had improved physical and psychological results when strengthening exercises were supplemented with amino acids [41].

### Post-viral fatigue syndrome

Post viral fatigue syndrome is characterized by prolonged weakness and other symptoms. These patients are not able to manage their routine deeds [42]. It is not just fatigue, but also more than that. They are sore throat, body aches, fluctuation of blood pressure, and gastrointestinal upsets, headaches, altered sleep pattern, and mental disturbances. Neurological symptoms such as new sensitivities or allergic reactions, and burning or prickling sensations in the limbs may be seen in some patients. Many patients may have anosmia and ageusia for prolonged period [43]. A key feature of the condition is that symptoms can suddenly worsen following only minimal physical or mental activity. These patients may experience sudden worsening of symptoms following minimal exertion. Post-viral fatigue symptoms are similar to chronic fatigue syndrome, which is also known as myalgic encephalomyelitis (ME). Hence, the WHO categorized it under neurological disorders. Nevertheless, not all cases of chronic fatigue syndrome are due to virus infection. Diagnosis of post-viral fatigue is purely based on symptoms and no diagnostic test is available [43].

There are some studies on post-viral fatigue in COVID-19 recovered patients. A study conducted in Italy found that about fifty-five percent of the hospitalized COVID-19 patients suffered at least three devastating symptoms, two months after their clear recovery from the original infection. In another study, nearly ten percent of patients who are infected with COVID-19 developed post-viral symptoms [9]. A Canadian study found twenty-one health-care workers from Toronto had post-viral symptoms for up to three years after catching SARS in 2003, and were not able to take up their routine work [44]. A study from Dubbo, Australia reported that eleven percent of patients (out of 253) developed chronic post-viral symptoms that lasted at least six months [45]. Several mechanisms are put forward for the development of post-viral syndrome. One of the mechanisms suggested is overactive immune system and resultant systemic inflammation. This theory is supported by increased serum levels of cytokines, which can reach brain and possibly cause long-term brain damage affecting the entire nervous system. Another mechanism put forward is an autoimmune component. The body immune system offers a rapid response, which can accidentally injure healthy tissue, disturbing all of the body's systems like the heart, brain, gastrointestinal tract etc. Further, the mitochondria, the energy source of the cells, are adversely affected by virus and may cause fatigue. Since no reliable diagnostic test is available, efforts are on to find

“biomarkers” in the body that can help with diagnosing the condition.

### Management of Fatigue:

Resting and relaxing are both essential components of any convalescence. As energy is required for both physical and mental activity, one should know not to exceed what one feels easy doing, stopping an activity when you are starting to feel more fatigued, and not carrying on with a task when you are tired. Finding the right balance on an individual basis between activity and rest is a process called pacing and many people find it helpful to alternate small flexible amounts of physical and mental activities with a longer period of rest/relaxation in between. Physical activities could include things like household tasks and going for a short walk when you feel ready to do so. Mental activities could include social activities with people you can still be in contact with, reading, listening to the radio, watching some TV, or doing a small amount of computer work. Do try to limit screen time on computers, phones and TV, and avoid using electronic devices to catch up on your normal work! Having established what is a safe baseline of physical and psychological activity that is not exacerbating symptoms, the subsequent step is to gradually try and increase the amount you are doing-while sticking to the rule of not exceeding limitations and living within what is called your ‘energy envelope’. Activity management needs to be done in a very flexible manner. So any increase in activity levels has to be steady and within your physical and psychological restrictions.

### 4. Continuing Covid-19 symptoms

Various studies conducted during the pandemic reported that elderly patients infected with COVID-19 have an increased risk for severity of the disease, the younger patients who are physically fit prior to infection also have symptoms months after acute illness [46, 47]. Researchers are trying to differentiate prolonged COVID-19 symptoms from sequelae following resolution of acute COVID-19 infection. This will help to define the post-acute and long-term phases of COVID-19, and distinguish health effects exclusively related to infection with SARS-CoV-2 from consequences of procedures and treatments required for care of persons with severe disease of any etiology. The common problems are myocardial inflammation, ventricular dysfunction (48,49), pulmonary function abnormalities (50,51), acute kidney injury [62], skin rash, alopecia (53,16), olfactory and gustatory dysfunction, sleep dysregulation, altered cognition, memory impairment (48, 54, 55, 53,56,57), depression, anxiety, changes in mood (53,54) etc.

### Other common complications

#### Covid-19 is leaving cured patients with brain fog

Brain is one of the most common organs affected by COVID-19. Many COVID-19 patients have complained of brain fog, a medical condition that disturbs mental capacity to

perform regular work. The common symptoms are mental confusion, delirium, difficulty in concentration, giddiness, difficulty in routine conversations, and loss of memory. A new study led by the US-based Indiana University School of Medicine covering nearly 4,000 Covid-19 survivors has found that more than fifty per cent of the people had one or the other form of brain fog-34% Memory loss; 28% difficulty concentrating; 31% Sleep disorder [58].

### Mechanism of Brain fog

A) Hypoxia – Virus makes copies in brain cells – these viral copies “steal away oxygen” from brain cells □ Headache, confusion, delirium

B) Triggered by "persistent immune activation" vasculitis

C) Encephalopathy: Altered mental function

### Post COVID-19 Skin lesions

The chilblain-like lesions could possibly be a late manifestation of COVID-19. To rule out, if the lesions are related to COVID-19, it is recommended to do a biopsy of them and to possibly perform a RT-PCR test, along with an IgM-IgG serological test on patients. These lesions can also help to diagnose COVID-19 patients who are asymptomatic [59].

### Suggested mechanisms for dermatologic manifestations:

The exact mechanisms of dermatological manifestations are not fully understood; however, a few plausible explanations have been suggested: (a) viral particles in cutaneous blood vessels lead to a lymphocytic vasculitis induced by immune complexes, which activate cytokines. Immune reaction to COVID infection activates Langerhans cells leading to vasodilation and spongiosis, (b) Accumulation of microthrombosis from other organs can reduce blood flow to cutaneous microvascular system [60].

### Conclusion

Since the starting of SARS-CoV-2, many clinical studies are in place to study various aspects of the disease, namely the signs and symptoms, course of the disease, acute and chronic complications, and treatment options including vaccine development. From the foregoing review, it is clear that majority of patients recover for the infection within two to six weeks, some percent of patients may have signs and symptoms for longer periods. This makes the patients not capable of doing the routine work as well as going to their regular work for quite some time may be up to six months or so affecting their economy very badly. As discussed earlier, there are involvement of various organs such as heart, lungs, kidney, brain, skin etc. Further, since the disease is continuing as pandemic, we may see other long-term complications in days to come. It is equally important to know that there is no definite treatment for all these complications other than complete rest and reassurance for majority of them. However, when the organ system is failing, definite intervention is required to save such patients.

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