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Long Haulers Effects of Covid-19 during Post-Covid-19

Khan I*,
Khan S,
Chermahini SH, and
Goderidze T

Department of Medicine, School of Health Sciences, The University of Georgia, Georgia

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***Corresponding Author:**
Irani Khan,
Department of Medicine, School of Health Sciences, The University of Georgia,
Kostava St. 77a, 0171 Tbilisi, Georgia

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1. Abstract

Most of the covid patients recover, but some of them can have long term covid health effects which includes different systems of the body. The symptom can persist from weeks to years and can vary patient to patient. There have been many research on the prodrome or the clinical course of SARS-CoV-2but a little attention has been given on the post covid manifestations. The reason for that could be the panic covid 19 created that made most focus on how to improve the ongoing symptoms and decrease the rate of mortality. Now that there has been mass vaccinations and the pandemic is almost over, we have more covid 19 survivors, thus the focus is also drawing on the debilitating long term health effects covid 19 has. The immune response by the human body to Covid-19 plays an important role in the disease progression and pathogenesis.

Covid 19 activates both anti-viral immune response as well as it initiates unregulated immune response by the release of the pro inflammatory cytokine which causes lymphopenia, abnormalities of monocytes and granulocyte. Because no official term has been established, long COVID may also be referred to as long-term COVID, chronic COVID, or post COVID syndrome.

2. Introduction

Covid 19 was declared as the global pandemic by WHO on the 11th of December [1] and as of 1st December 2022 - 639,132,486 cases have been reported among which 6,614,082 have died [2]. A lot of people with COVID-19 recover completely and return to their normal self although, there are some people that experience symptoms and perhaps other complications several weeks or months after being infected with covid 19 [3] these are called long covid haulers. The post- COVID-19 condition lasts for more than 12 weeks [4]. In October 2020 United Kingdom announced that 10-20% patients continue to have symptoms or complication one month after the diagnosis. [5] According to an Italian study, 87% of people who were recovered and discharged from hospitals still had at least one symptom after 60 days.[6] According to a study Four months after being infected with SARS-CoV-2, 42% of people had ten or more long COVID symptoms, and 60% had severe long COVID symptoms.[7]

Long COVID is a multifaceted illness characterized by a wide range of symptoms. [8] The main systems involved are cardiovascular system, respiratory system, central nervous system, genitourinary system, gastrointestinal system. It includes cluster of around 50 symptoms [9] among which concerning symptoms include: chest pain, dyspnea, palpitation, joint pain, muscle weakness, hair loss, anxiety, cough, sleep disturbance, fatigue, loss of taste and smell, diabetes, cognitive dysfunction b [10].

Coronavirus-19 binds to the receptor of the angiotensin converting enzyme which is considered to be one of the most important enzymes in the human body and it works on multiple systems. Thus, by binding of the covid 19 with this receptor it not only hampers the receptor activity but also causes dysfunction of the organs which includes kidney, vasculature, lung, heart [11]. In covid-19, cytokine storm has been associated with the increase in severity and progression of the disease which can result in severe complications or even death. The cytokines that are mainly seen are: FN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α and TGF-β [12].

In many post covid patient, mast cell activation syndrome [MCAS] has been seen [13]. Mast cell activation syndromes [MCAS] is an excessive production of abnormal MCs. [14] MCAS mainly involves: cardiological, GIT, pulmonary, neurological and dermatological problems.[15]

In this review paper, we look into the available data on the post-COVID-19 condition study, with the main goal of 1] post covid mechanism 2] summarizing of clinical manifestation of post covid syndrome 3] possible approach for post covid syndrome diagnosis and management.

3. Post COVID Mechanism

1. Cytokine storm.

2. Ace 2 receptor and covid19 manifestations.

3. Age related.

3.1. Cytokine Storm

Cytokine storms are linked to the severity and progression of COVID-19. They can cause severe complications like acute respiratory distress syndrome [ARDS] and multi-organ failure that are the most common causes of death from the disease [16]. The severity of COVID-19 disease is thought to be connected to viral-induced cytopathogenic effects and virus escape from the host's own immune system the host immune system can create a fatal inflammatory condition known as CRS in COVID-19 individuals. This is a phenomenon of an excessive inflammatory response in which inflammatory cytokines are quickly released in huge amounts in response to infectious stimuli [17]. Inflammatory cytokine storm is a serious condition that requires intensive care unit [ICU] admission [18]. The possible reason for such an immense cytokine release has not been known till now but some hypotheses have been given. For the same the first one being that: 1] Cell Pyroptosis: Pyroptosis is a form of proinflammatory cell death that is controlled by gasdermin. This form of necrotic of cell death involves cell swelling and lysis and results in ion fluxes and the release of proteins from the interleukin [IL] family. Pyroptosis causes peripheral lymphopenia in COVID-19 patients by triggering the production of pro-inflammatory cytokines and impairing macrophage and lymphocyte activities. Many cytokines are increased in number but the leading cause of inflammatory response in COVID-19 is IL-6. [19]. The second hypothesis is the development of neutralizing antibodies[NAb] against the virus's surface antigen. The severity of the disease is significantly associated to NAb levels and anti-S IgG titres. NAb levels in COVID-19 patients who have recovered are related to the severity of lung damage [20].

3.2. Ace 2 Receptor and Covid19 Manifestations

SARS-CoV-2 is 80% identical to exploit the angiotensin-converting enzyme 2 [ACE2] as a cellular entrance point. ACE2 expression is detected in many cells: In CVS: myocardial cells, endothelial cells, artery smooth muscle cells. In respiratory system: type II alveolar cells, bronchial transient epithelial secretory cells, respiratory epithelial cell. In GIT: esophagus epithelial cells, tongue epithelial cells, stomach, cholangiocytes, adipose tissue, pancreatic exocrine glands and islets, enterocytes from ileum and colon and rectum cells. In nervous system: neurons and glia. In GUT: renal proximal tubule cells, podocytes, bladder urothelial cells, testis [Leydig and Sertoli cells and spermatogonia], uterus epithelial cells, ovary and breast, maternal–fetal interface [21]. The tissues with >1% of the ACE2 expression are considered to be high risk tissues and they include ileum [30%], heart [> 7.5%], kidney [4%], bladder [2.4%] lower respiratory tract [2%], lung [> 1%] [22].

The lungs have a high RAAS activity and ACE2 counteraction is essential to homeostasis. Because SARS-CoV-2 targets AT2 cells, the infection disrupts the ACE/ACE2 physiological balance, and local Renin - angiotensin - aldosterone overactivation causes increased capillary permeability and edema [23]. In terms of internalization, SARS-CoV-2 competes with Ang II for ACE2. The binding, on the other hand, inhibits ACE2 activity and so lowers enzyme expression in the membrane [24]. Downregulation of ACE2 promotes ACE/ACE2 imbalance and enhances activation of the ACE/Ang II/AT1R axis, resulting in an increase in Ang II-mediated vascular constriction [25]. The female reproductive system expresses ACE2, which might be a target for SARS-CoV-2. Pregnant women are thus a high-risk category for COVID-19 [26]. . Because ACE2 is prominently expressed in the testicles, it raises concerns about the virus's impact on fertility and sexual transmission. [27].

3.3. Age Related Manifestations

Age has been identified as a key cause of COVID-19-related mor-

tality, with a specific influence on the demographic structure of the population in nations with a larger number of elderly people.

Post-Acute COVID Syndrome presentation Prognosis and long-term outcomes will have distinct features in the older adults. It is hypothesized that in the setting of COVID-19 illness in older people, a pre-existing decrease in the total number of naïve T cells and an increase in memory T cells may explain a higher risk of severe clinical presentation and worse prognosis. Patients with Alzheimer's disease, for example, have a diminished ability to return to their pre-COVID condition, with a progression of their functional impairments [28]. In the largest study of its kind, published recently in the journal BMJ Researchers estimated that 32% of older persons in the United States who survived covid infections had extended covid symptoms up to four months after infection — more than twice the 14% prevalence seen in a previous study of adults aged 18 to 64 [29].

Older individuals are a high-risk demographic for significant acute respiratory syndromes, necessitating vigilant monitoring of their health. 6. The literature reveals varying degrees of somatic, pulmonary, and psychological impairment among Covid-19 patients, particularly among the elderly [30-32].

According to the China National Health Commission, mortality primarily affects older persons, as the median age of the first 17 fatalities up to January 22, 2020, was 75 years. Because COVID-19 appears to have a pathogenic potential comparable to SARS-CoV and MERS-CoV, older persons are likely to be at an elevated risk of severe infections, a cascade of problems, disability, and death, as seen with influenza and respiratory syncytial virus infections [33]. The geriatric population are particularly vulnerable to COVID-19. Predisposition and terrible consequences increase the dangers for the elderly. The key variables for COVID-19 susceptibility have been identified as older age and underlying illnesses. The age of ≥60 is a significant risk factor. The physiological functioning of various important organs and innate/adaptive immune defense have also been linked to aging. Furthermore, infection acquisition is more likely in the presence of underlying chronic conditions. Older COVID-19 dementia patients may experience moderate and unusual symptoms such as diarrhea or sleepiness. Such elderly and fragile individuals, however, have a lower probability of surviving the COVID-19 infection. Higher Sequential Organ Failure Assessment score and elevated d- dimer [>1 g/mL] were shown to be indicators for an increased risk of mortality in older COVID- 19 patients. A comprehensive age-specific analysis of COVID-19 symptoms has not been undertaken. However, like with other illnesses, the probability of non-specific and unusual clinical signs in older people is strongly anticipated [34].

4. Cardiac Dysfunction

SARS-CoV2 infection can have structural and functional effects on all organs [35]. COVID-19 infection affects a variety of organ systems, including cardiovascular system. Long-term follow- up reveals an elevated risk of heart failure, myocardial fibrosis, acute coronary syndrome, arrhythmia, hypertension, and right ventricular dysfunction. After hospital release, there is an increase in mortality in COVID-19 patients, and early myocardial damage is related with an increase in death [36].

A large analysis from the US Department of Veterans Affairs [VA] databases recently demonstrated an excess burden of cerebrovascular disorders, arrhythmia, ischemic heart disease, heart failure, and thrombotic disorders between 30 days and 12 months after COVID-19 infection in comparison to control cohorts. An analysis of data from the US Department of Veterans Affairs [VA] databases recently revealed an increased burden of cerebrovascular disorders, arrhythmia, ischemic heart disease, heart failure, and thrombotic disorders in comparison to control cohorts between 30 days and 12 months after COVID-19 infection [37].

In the lack of comprehensive primary data on the long-term cardiovascular sequelae of COVID- 19 infection, available data on other viral illnesses can provide insights and direction. The SARS-CoV-caused severe acute respiratory distress syndrome in 2002-2003 was also a worldwide health problem. These patients' long-term follow-up indicated hyperlipidemia, aberrant glucose metabolism, and cerebrovascular catastrophe [CVA]. These findings show that post-infectious COVID-19 individuals are at higher risk for cardiovascular events and metabolic problems, which we have already begun to see (Figure 1).

One-fourth of hospitalized patients had myocarditis even three months after being discharged from the hospital. Most medical experts still believe cardiac issues caused by COVID-19 to be an uncommon occurrence, especially in compared to the neurological and pulmonary symptoms found in patients who have previously been infected with COVID. While much more analysis and research is needed to produce conclusive results, current evidence clearly shows that many patients who had previously contracted COVID-19, whether it was an asymptomatic case or a severe one requiring hospitalization, may suffer from long-term heart issues as a result of their infection [38].

5. Respiratory Manifestations

Long-term follow-up of survivors from earlier coronavirus epidemics revealed deterioration in pulmonary function tests [PFT] that lasted months to years after recovery [39].

Many long-term pulmonary problems have been reported with COVID-19 infection. Dyspnea, ventilator dependency, oxygen dependence, pulmonary function test [PFT] abnormalities, and fibrotic lung disease are examples of these. Dyspnea is the most prevalent pulmonary symptom reported after COVID-19, and it might last for 2 months in 22.9%-53% of patients [40]. One of

these impacts is scarring of lung tissue, known as fibrosis, which impairs the exchange of oxygen and carbon dioxide in the lungs as well as the general elasticity of the tissue [41]. Oxygen dependence has been documented in up to 6.6% of hospital discharged survivors [40].

A study by the Hong Kong Hospital Authority conducted in March 2020 found that the virus can take a toll of as much as a decrease of 20-30% in lung capacity in some case

According to March 2020 research undertaken by the Hong Kong Hospital Authority, the virus can cause a 20-30% loss in lung capacity in some cases. Research published in the Journal Radiology from August to December 2020 identified anomalies on a hyperpolarized xenon MRI [XeMRI] scans of the lungs in COVID-19 patients with decreased oxygen uptake for more than three months and, in some cases, nine months after leaving the hospital while other clinical parameters were usual (Figure 2).

Patients with pre-existing respiratory disorders had a considerably greater death rate, according to Lohia et al., 2021. As a result, there is a larger requirement for ICU hospitalization and mechanical ventilation than in individuals without pre-existing respiratory problems. The degree of persistent functional abnormalities is affected by a variety of factors, including the patient's age, comorbidities, smoking history, length of hospitalization, the severity of the acute condition [such as the necessity for ICU care], and the type and quality of therapy provided [41].

A more in-depth qualitative investigation of a smaller number of participants, maybe using alternative methodological techniques such as questionnaires and focus groups, could give a complementary viewpoint on the current study's findings in the future [39].

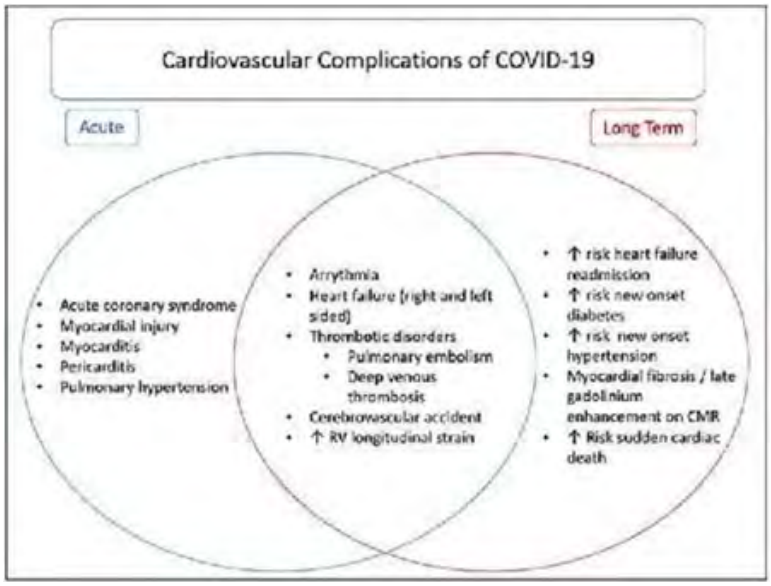

Figure 1: COVID-19 infection causes both acute and long-term cardiovascular problems. [36]

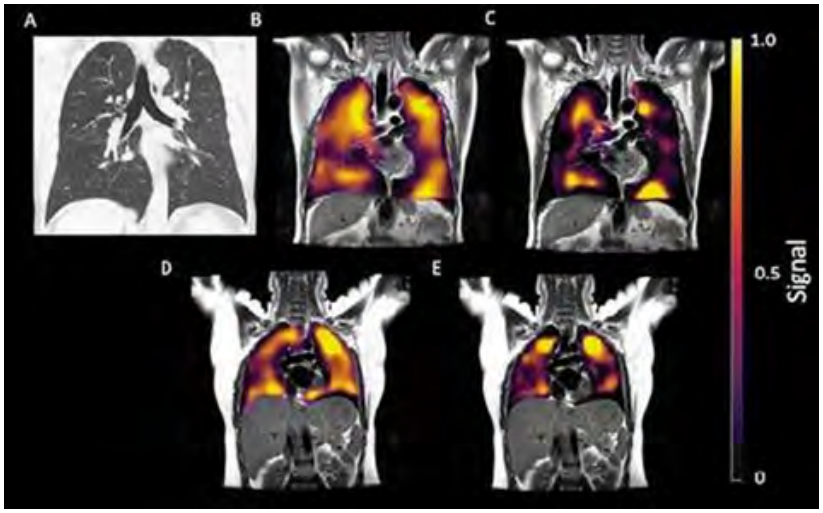

Figure 2: Images taken 172 days after discharge in a 60-year-old patient with a history of dyspnea following COVID-19 [top row]. CT, breathing, and red blood cell [RBC] phases of hyperpolarized xenon 129 MRI [A–C] [XeMRI]. Images of a healthy control volunteer [bottom row] during the gas and RBC stages. Both individuals' XeMRI images are displayed in coronal view, with damaged RBC in the patient.

6. Anosmia in Post Covid Patients

Symptoms of the neurological system persist in COVID haulers even after individuals recover from COVID-19. Anosmia, or loss of smell, is the most prevalent sensory deficit during the disease's progression and is caused by olfactory dysfunctions [42]. According to many meta- analyses, more than 50% of COVID-19 patients have olfactory dysfunction during the early stages of the disease or even months after recovery. More than 10% of COVID-19 infected people may experience persistent anosmia, which can last for more than a year [42]. Earlier, smell loss was more likely in asymptomatic COVID-19 instances than in severe cases.

According to one study, individuals with OD recovered better in terms of hospitalization and death rate. Age is regarded as a significant risk factor in COVID-19-related olfactory dysfunction [42].

According to the most recent literature research, a significant proportion of COVID-19 patients have anosmia symptoms for which the cellular and molecular origins are unknown [43]. Affected individuals are frequently concerned since these deficiencies can lead to hygiene issues such as body odor [44]. The study found a substantial association between sex, age, smoking, and ACE2 and TMPRSS2 expression, implying that men, elders, and smokers had a higher prevalence of olfactory dysfunction than females, youngers, and nonsmokers [42]. While many factors in the nasal microenvironment affect olfactory dysfunction, including viral titer, pre-existing inflammatory condition, or immune-deficiency, it may also be linked with individuals' genotype, i.e., genetic factors may determine the prevalence and potential consequences of COVID-19 associated olfactory [42]. Although the precise pathophysiology of anosmia is uncertain, multiple studies point to a variety of possible reasons [43].

According to reports, the two primary genes responsible for CoV-2 access into host cells are TMPRSS2 and ACE2. These are not found in the olfactory epithelium; instead, they are found in supportive olfactory cells, stem cells, and perivascular cells, the sustentacular cells, or the supporting cells which cushion the olfactory receptor neurons. As a result, any injury to the sustentacular cells might result in olfactory impairment. This suggests that non-neuronal cells are involved in COVID-19's modifications in smell perception [43].

SARS-CoV-2 is a human respiratory coronavirus that penetrates cells by attaching to the angiotensin-converting-enzyme 2 [ACE2] receptor on the host. The presence of high ACE2 expression in type II alveolar cells suggests that the lungs are the primary location of SARS- CoV-2 infection. SARS-CoV-2 can enter the olfactory bulb and neurons through ACE2 receptors found in the olfactory epithelium. The invasion of SARS-CoV-2 into the olfactory bulb might result in apoptosis of the olfactory epithelium and a reduction in the volume of the olfactory bulb, thereby producing the symptom of olfactory dysfunction [45].

Because of the high presence of ACE-2 receptors in non-neuronal olfactory epithelium cells, it is likely that COVID-19 targets nasal system cells rather than olfactory neurons. As a result, in circumstances when the virus destroys the OE, the olfactory may quickly heal and recover [43]. Because the olfactory epithelium has a high level of ACE2 receptors, inflammation in this area might be one of the major causes of anosmia. Despite the lack of ACE2 receptors in olfactory receptor neurons, inflammation can travel to olfactory receptor neurons or stem cells via supporting cells and affect the olfactory bulb as well as the central nervous system, resulting in a loss of smell sensibility [43].

Three mechanisms for anosmia in COVID-19 patients were reported by certain authors: i] local infection of support cells and vascular pericytes in the nose and olfactory bulb, which may impair the function of bipolar neurons or mitral cells; ii] damage to sensory epithelial support cells, which may impair the communication route from sensory neurons to the brain indirectly; iii] Sustentacular cell and Bowman's gland cell injury that might lead to diffuse olfactory sensory epithelial morphological damage and altered smell perception [46].

According to the suggested study and the growing body of data, anosmia should be included to the list of symptoms used in screening tools for probable COVID-19 infection, even if additional research is needed. Ignoring this symptom by public health institutions is no longer acceptable [43].

The efficacy of therapy choices is not stated at this time, although few therapies have shown to be capable of resolving the condition of olfactory dysfunction [43]. According to a French Society of Otolaryngology publication, patients should avoid corticosteroids for the treatment of SARS-CoV-2 infection [46]. Clinicians, on the other hand, routinely employ empirical oral steroids to reduce inflammation and edema in the treatment of anosmia. Given the elevated risks of immunosuppression associated with these medicines, we believe that tailored case management and therapy should be used [46].

7. Management

Management methods for post-COVID sequelae will differ widely based on the symptomatology and demands of each individual patient. Because COVID-19 is an infectious illness that predominantly affects the lung, its multi-organ involvement necessitates a multidisciplinary approach that includes almost every discipline of internal medicine and geriatrics During the first visit of the patient general assessment, venous sampling, electrocardiogram, clinical history, and infectious disease assessment should be done. During the second visit gastroenterology, pneumology rheumatology, otolaryngology and ophthalmology should be tackled. During the third visit ultrasound, neurology, psychiatry, pediatric nutrition in-

ternal medicine and geriatrics along with Chest X-ray and or chest CT scan should be investigated. In this way all the interdisciplinary team get together [47].

Infectious disease assessment: One of the most pressing issues to address is the likelihood of SARS-CoV-2 reinfection. According to some accounts, COVID-19 might return in people who were thought to have fully recovered from the condition [48].

There is relatively little data on COVID-19 clinical history after the acute phase, and not much is known about the mid- and long-term result. It is consequently critical that medical services be put in place to guarantee a thorough follow-up of patients released from hospitals and ER departments. Patient follow-up will also provide an exceptional chance to collect data in a consistent manner to further quantify COVID-19's worldwide impact.

8. Conclusion

The main purpose of this review article was to give some information about the post covid haulers as not much data is available. At present, there are many studies goings on whose whole purpose is to understand the post covid acute syndrome [PCAS]. It barely has been three years since the covid-19 outbreak, and experts still don't know enough about the disease's long-term effects on every system in the human body. The information and data gathered this far have shown to be extremely valuable in understanding some elements of this syndrome and the constant input of fresh information regarding post covid acute syndrome has provided an increasing push to the research to continue investigating. Because this condition is new, it is too early to know everything about it, although studies are being conducted on a bigger scale.

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