



UNDERLYING FACTS AND MANAGEMENT OF POST COVID-19 SYNDROME – A GLOBAL SCENARIO

Dr. Satyendra Kumar Sinha
Assistant Professor & Head
Department of Zoology
Ram Jaipal College,
Jai Prakash University, Chapra

ABSTRACT

SARS-CoV-2 is primarily responsible for COVID-19, a respiratory virus infection. COVID-19 is currently regarded as a systemic disease, because of the involvement of several organs in individuals infected with SARS-CoV-2. The initial effects of COVID-19 are well known and frequently involved a rise in mortality. However, long-term or delayed COVID-19 problems (post-COVID-19 syndrome) are now more commonly understood and are linked to higher morbidity. The major symptoms of post-COVID-19 syndrome include dyspnea, fatigue, dysgeusia, anosmia, chest pain, arrhythmias, headache, lightheadedness, and brain fogging (cognitive impairment), which lead to enhanced morbidity and a low-quality life. Treatment and management are well required for these long COVID haulers. The role of the interprofessional collaborative team in the assessment and management of patients with post-COVID-19 syndrome is a highlight of this paper. The purpose of this review is to explain the frequency of delayed and persistent symptoms, system-based symptoms, ways to recognize symptoms and indicators to manage the condition, and the role of an interdisciplinary collaborative approach in the management of post-COVID-19 syndrome in. To achieve this, several research papers were analyzed and evaluated that resulted into the outcome as interprofessional team of clinicians, specialists, super specialists, occupational therapists, social workers, and self-training programs is required to work and collaborate on improving and overcoming post COVID-19 syndrome. Unmanaged long COVID haulers may be subject to complex morbidity and may contribute to gross mortality.

KEY WORDS

SARS CoV-2, Post COVID-19 Syndrome, Long COVID-Haulers, Dyspnea, Anosmia, Dysgeusia, Arrhythmias, Brain fogging.

INTRODUCTION

Since the first case were discovered in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19), a viral respiratory illness brought on by the novel coronavirus SARS-CoV-2. It caused significant morbidity and mortality throughout the world. Approximately 5% to 8% of infected individuals developed hypoxia, bilateral lung infiltrates, and impaired lung compliance requiring non-invasive ventilation (NIV) or mechanical ventilatory support, even though the majority of COVID-19 patients are asymptomatic or have a mild to moderate illness.(1) The management of COVID-19 is mainly supportive, still many therapeutic agents such as antivirals (Remdesivir), monoclonal antibodies (e.g., Sotrovimab), anti-inflammatory drugs (dexamethasone, methylprednisolone), and immunomodulatory drugs (Baricitinib and Tocilizumab) are accessible under emergency use authorizations (EUAs) for the treatment of COVID-19, but their effectiveness relies on the timing, severity, and other risk factors of the disease.(2) The earlier epidemic SARS-CoV and MERS-CoV left people who recovered from these viral illnesses with lingering symptoms of extreme fatigue, persistent shortness of breath, behavioral health issues and decreased quality of life (QOL). As a result, the epidemics placed a significant burden on the local healthcare systems where they occurred. Similarly, despite biochemical evidence that the replication of SARS-CoV-2 ceases to exist four weeks after the initial infection (based on the sampling of viral isolates from the respiratory tract and not the nasopharyngeal or oropharyngeal specimen), a constellation of various clinical symptoms known as post-COVID-19 syndrome has been described in a minor proportion of patients who recovered from SARS-CoV-2-induced COVID-19. The syndrome known as post-COVID-19 is characterized by the continued presence of clinical symptoms more than four weeks after the start of acute symptoms. "Post-Covid conditions" are a term coined by the Centers for Disease Control (CDC) to identify health problems that last longer than four weeks after contracting COVID-19. These consist of Persistent post-covid syndrome (PPCS) or long-covid (which includes a wide variety of symptoms that might last weeks to months). COVID-19's impacts on several organs lead to hospitalization and treatment for COVID-19 effects. The common clinical signs of "long COVID" are weariness, brain fog, headaches, chronic loss of taste or smell, coughing, depression, low-grade fevers, palpitations, disorientation, muscular discomfort, and joint pain. Clinical signs relating to the cardiovascular, pulmonary, renal, and neuropsychiatric organ systems are among the multisystem effects of COVID-19, although it is unknown how long these effects will last. Similar to other serious illnesses, the long-term effects of COVID-19 treatment or hospitalization are presented as post-intensive care syndrome (PICS), resulting in weakness and post-traumatic stress disorder. Many patients who are suffering from COVID-19 problems are improving over time. Based on the severity of symptoms following infection with COVID-19, Nalbandian et al. categorized post-acute COVID-19 as subacute or persistent (lasting up to 12 weeks after the initial acute episode) and chronic or post-Covid-19 syndrome (persisting beyond 12 weeks). It should

not, however, be attributed to a different diagnosis. ((3) This review paper discusses post-COVID-19 syndrome prevalence, system-based manifestations, pertinent clinical investigations, treatments, and the value of an interprofessional team approach.

CAUSE OF POST COVID SYNDROME

The actual cause of post-COVID-19 syndrome is unknown and likely complex given the scant published evidence on this novel clinical entity, especially given the involvement of numerous organ systems. An excessive immune response known as systemic inflammatory response syndrome (SIRS) and a protracted compensatory, counterbalancing anti-inflammatory cascade known as compensatory anti-inflammatory response syndrome (CARS) are the human body's reactions to any serious infection or trauma. (4) The immediate clinical result and eventually, the infection-related prognosis is a fine balance between SIRS and CARS. Patients with underlying comorbidities or immunocompetent environments may experience a "cytokine storm," that is the term for an excessive release of cytokines. Chronic cytokine release leads to multiple organ failure, acute respiratory distress syndrome (ARDS), hypercoagulable conditions, ACE-2 pathway maladaptation, hypoperfusion to end organs, septic shocks, and ultimately death. Clinical improvement or viral reactivation, secondary infections, and death will ensue from immunologic hemostasis between immune activation and immunosuppression. (5)

EPIDEMOLOGY

Based on the scant information from several observational and prospective cohort studies from China, France, Spain, the United Kingdom, the United States, and Italy that assessed the long-term effects of COVID-19, it was figured out that patients affected by COVID-19 who required ventilator support or ICU admission were more likely to develop post-COVID-19 syndrome. Obesity, advanced age, and pre-existing pulmonary diseases are all thought to enhance the chance of developing post COVID-19 syndrome in patients.(6) The severity of COVID-19 is more likely to affect people who already have pre-existing conditions like diabetes mellitus, chronic kidney disease (CKD), chronic cardiovascular disease, underlying malignancies, organ transplant recipients, and chronic liver disease, as has become increasingly obvious as this pandemic has progressed. The incidence of these concomitant illnesses as risk factors in post-COVID-19 syndrome, however, is not yet known. (7) At 6-month follow-up, female COVID-19 patients were more likely to exhibit post COVID-19 syndrome symptoms, including fatigue, anxiety, and sadness. (8) There are few studies examining racial and ethnic factors in post COVID-19 syndrome. According to Halpin et al., 42.1% of Black Asian and Minority Ethnic (BAME) participants reported moderate to severe dyspnea, compared to 25% of white patients, in their study evaluating post-COVID-19 symptoms 4 to 8 weeks following hospital release. (9)

HISTOPATHOLOGY

A multisystem-affected biomedical condition called post-COVID-19 syndrome frequently impacts the hematological, cardiovascular, and respiratory systems. To a lesser degree, the neuropsychiatric, renal, and endocrine systems are also involved. The following is a description of significant organ-specific histopathological findings.

LUNGS

The COVID-19 lung autopsy revealed diffuse alveolar damage in all stages, including focused and organized fibroproliferative diffuse alveolar damage resembling ARDS. ((10) Rarely, Myo fibroblastic growth, mural fibrosis, and microcystic honeycombing were also observed. Lung tissue examination (autopsy and explanted lungs of lung transplant recipients) with severe COVID-19 pneumonia revealed histology similar to end-stage pulmonary fibrosis without active SARS-CoV-2 infection, indicating that some individuals may acquire lung fibrosis after active infection has cleared up. When compared to ARDS caused by influenza, the severity of endothelial damage and microthrombi found on lung autopsies in SARS-CoV-2 infection is much higher. (11)

HEART

Histopathologic analysis of COVID-19 myocardial insults shows a considerable variation. In the cardiac tissue of 62% of acute COVID-19 autopsy cases, the virus genome was found. (12) The gold standard for determining whether a patient has myocarditis is endomyocardial biopsy. According to the 1987 Dallas criteria, viral myocarditis is consistent with lymphocyte infiltration and myocyte damage without ischemia. Endomyocardial biopsy, however, barely detects 10% to 20% of myocarditis in post-acute COVID-19 syndrome. Sampling error is a secondary cause of this low sensitivity. Endomyocardial biopsy results from immunohistochemical analysis revealed severe intramyocardial inflammation and an increase in perforin-positive cells. Macrophages, T lymphocytes, and CD45R0 T memory cells are all more prevalent. Cell adhesion molecules (CAMs) such as CD54 and ICAM-1 are more prevalent. (13)

BRAIN

The cerebrum and cerebellum of every patient were shown to have acute hypoxia injury in a single-center histopathological analysis of brain specimens taken from 18 patients who passed away with COVID-19. Notably, no features of encephalitis or other specific brain changes were observed. Furthermore, cytoplasmic viral staining was not detected in the brain tissue after immunohistochemical investigation. (14)

RENAL

Acute tubular necrosis was the main finding in the kidney biopsies from which SARS-CoV-2 was isolated. Specific to COVID-19-associated nephropathy (COVAN) are collapsing variant localized segmental glomerulosclerosis, acute tubular damage, and global tuft involution. (15)

CASE STUDY & STATUS

During a 60-day follow-up of 488 patients following hospitalization for acute COVID-19, the most frequently reported symptom was dyspnea, followed by cough and loss of taste or smell in 32% of patients. This observational cohort study also revealed a mortality rate of 6.7% and a readmission rate of 15%. (16) In a different study that followed 110 COVID-19 patients for 90 days after their hospitalization for acute COVID-19 were discharged, the most prevalent symptoms were fatigue and dyspnea (39%), followed by sleep disturbance (24%), chest discomfort (12%), and cough (11%). (17) evaluation of 1733 patients as part of a 6-month follow-up study by Huang et al. found that fatigue (63%) was the most prevalent symptom, followed by sleep difficulties (26%), depression, anxiety (23%), and hair loss (22%). At 6-month follow-up, patients who were hospitalized with severe acute respiratory failure caused by COVID-19 were thought to have reduced pulmonary function and abnormal chest imaging. According to the aforementioned studies, at least 25% or more of the study participants experienced exhaustion, shortness of breath, psychological stress (anxiety, depression), posttraumatic stress disorder, poor attention, and aberrant sleep patterns.

PULMONARY SIGNS AND SYMPTOMS

We still do not know how serious and long-lasting COVID-19 infection is. However, data indicate that many individuals continue to experience respiratory symptoms weeks to months after receiving a COVID-19 diagnosis. Endothelial and epithelial damage brought on by monocyte and neutrophil invasion that results in ARDS is induced using both viral-dependent and independent processes. The most prevalent physiological abnormality in post COVID-19 is a decrease in diffusion capacity, which is inversely correlated with the severity of the disease. The persistence of ground-glass opacities is the most frequent finding of post COVID-19 on high-resolution lung CT. Patients with post COVID-19 syndrome frequently have dyspnea, cough, oxygen reliance, difficulty weaning from mechanical ventilation or NIV, fibrotic lung alterations, decreased diffusion capacity, and diminished endurance. The most common pulmonary symptom in post COVID-19 (40% to 50% prevalence at 100 days) is dyspnea. The shortness of breath caused the average 6-minute walking distance to be considerably lower than the usual reference at a 6-month follow-up. At 60-day follow-up, about 6% of patients still require more oxygen. (16) According to a Spanish study, at the 30-day follow-up post-discharge, 50% of tracheostomy patients were successfully weaned off their devices. (18) At the 6-month follow-up, almost 50% of patients have at least one abnormal CT chest finding (fibrotic alterations, ground-glass opacity).

CARDIOVASCULAR SIGNS AND SYMPTOMS

The most frequent mechanisms of cardiovascular damage include direct virus-mediated cytotoxicity, ACE-2 receptor downregulation, and immune-mediated inflammation affecting the myocardium and pericardium. These symptoms include dyspnea, fatigue, myocarditis, decreased cardiac reserve, dysregulation of the renin-angiotensin-aldosterone system (RAAS), autonomic dysfunction and arrhythmias. (19)

HEMATOLOGIC SIGNS AND SYMPTOMS

Compared to consumptive coagulopathy from disseminated intravenous coagulation (DIC), acute COVID-19-related thromboembolism is secondary to the hyper-inflammatory and hyper-coagulable state. (20) In acute COVID-19, thromboembolism is disproportionately high due to hypoxia, endothelial damage, platelet activation, and pro-inflammatory cytokines. In the post-COVID-19 period, the persistence and intensity of this hyper-inflammatory state enhances the possibility of thrombotic consequences.

NEUROPSYCHIATRIC SYMPTOMS

It is hypothesized that direct viral-mediated neurotoxicity, systemic inflammation, and microvascular thrombi are some potential processes causing neuropathology in COVID-19. Cognitive dysfunction in post-COVID-19 may be influenced by dysautonomia, deconditioning, and post-traumatic stress disorder, leading to brain fogging. Long-term cognitive damage in post-COVID-19 patients is considerably exacerbated by prolonged intubation and ICU stays. (21)

RENAL SIGNS AND SYMPTOMS

Acute kidney injury (AKI) and requirement for kidney replacement therapy (KRT) were relatively common features of severe COVID-19, especially in patients admitted to the intensive care unit, with up to 25% incidence; furthermore, both were important predictors of survival. (22,23) Approximately 28% of hospitalized COVID-19 patients were also affected by AKI and 9% of them required KRT. (24) At discharge, most of them did not need dialysis.

ENDOCRINE SIGNS AND SYMPTOMS

Post COVID-19 endocrine symptoms are influenced by viral infection, inflammation, and immunologic damage. Several weeks after the acute COVID-19 symptoms subsided, isolated case reports of Diabetes Ketoacidosis (DKA), subacute, and Hashimoto thyroiditis were published. (25,26) Loss of bone mass density (BMD) by demineralization during acute and post acute recovery from COVID-19 may be exacerbated by immobility, steroid use, and a lack of vitamin D3.

MULTISYSTEM INFLAMMATORY SYNDROME IN ADOLESCENT

A new clinical entity known as MSIS affects people under the age of 21 who have recently or currently been infected with the SARS-CoV-2 virus and is characterized by fever, multiorgan dysfunction, and elevated inflammatory markers. Acquired immunological responses from complement activation, the production of autoantibodies (viral host mimicry), and excessive cytokines from T-cell stimulation are the most likely underlying mechanisms. (27)

ASSESSMENT OF DISEASE

During the follow-up visit, the treating professionals must obtain a thorough clinical history of the beginning and duration of the current symptoms, underlying medical comorbidities, the severity of COVID-19 and medication history. If applicable, hospitalization records of COVID-19-related admissions must be carefully examined, including the relevant diagnostic tests performed and length of hospitalization. Since post COVID-19 syndrome is a developing clinical condition, there are no such precise recommendations for managing it at the moment. However, this unusual clinical entity should be treated as a diagnosis of exclusion until more information is available. First, all additional COVID-19-related problems and acute alternative diagnoses must be checked using the proper laboratory and radiological evaluations. SARS-CoV-2 reactivation and relapse have been documented in many case reports in COVID-19-recovered patients. Hence, it is also necessary to rule out any more post-viral secondary bacterial and fungal infections or viral disease. (28) All patients should undergo a routine laboratory evaluation that includes a complete blood count (CBC) and a comprehensive metabolic panel (CMP), which includes tests for renal, liver, and coagulation function. If clinically necessary, additional tests such as C-reactive protein (CRP), fibrinogen, D-dimer, troponin, and ferritin can also be taken into consideration. (29) Patients who present primarily with respiratory symptoms may receive help from repeat pulmonary imaging, preferably with a high-resolution CT scan (HRCT) or CT angiogram. (30) To rule out an underlying cardiopulmonary disease, cardiac function tests such as EKG and echocardiography must be considered. If clinically necessary, patients presenting with vascular (CT/MRI) and cognitive tests must undergo neuroimaging.

TREATMENT & MANAGEMENT

Post-COVID-19 syndrome can be seen as a multisystem illness that frequently presents with respiratory, cardiovascular, hematologic, and neuropsychiatric symptoms, either separately or in combination. As a result, the therapy must be tailored to the patient and use an interdisciplinary strategy to address both the clinical and psychological components of this condition. Major medical hospitals around the world are now developing post-COVID care clinics, that offer multidisciplinary examinations and services for individuals recovering from COVID-19. Treatment should be maximized for comorbid illnesses like diabetes, cardiac ailment, chronic renal disease, and hypertension (29,31) Patients should be instructed on how to self-monitor at home using instruments that have been approved by the FDA, such as blood pressure, blood glucose, and pulse oximeter. Patients should be urged to practice good sleep hygiene, eat a balanced diet, drink in moderation, and give up smoking. (29) When necessary, simple acetaminophen (paracetamol) analgesia should be considered. Provided there are no other contraindications, a planned yoga exercise program with aerobic and resistance components must be recommended. (32)

PULMONARY

Patients who recovered from COVID-19 but are still experiencing signs of pulmonary complications should be assessed and closely monitored by a pulmonologist at the earliest possible time. Enrollment in a rehabilitation program concerned with pulmonary ailments is essential for a faster recovery. Vaccination against the flu and Streptococcus may be beneficial for patients who experience chronic symptoms. If clinically necessary, a 6-minute walk tests and pulmonary function tests should be considered. Steroid use in post-COVID-19 patients is uncertain, and there is scant information on how well it works in these patients. Although a small study analyzing COVID-19 patients for 4 weeks after discharge found that early steroid induction resulted in a rapid and considerable recovery. (33) Additional clinical studies are necessary to assess its efficacy in Post COVID-19 patients.

CARDIOVASCULAR

Patients who recovered from COVID-19 but still experiencing cardiac symptoms must be monitored by a cardiologist. To rule out any heart ailments such as heart failure, fibrillation, ischemic heart disease and arrhythmias, cardiac function tests such as echocardiogram and echocardiography must be performed. Additionally, an MRI of the heart might be considered to check myocardial fibrosis if needed as in post covid-19 patient prevalence of myocardial fibrosis is well reported.

HEMATOLOGIC

Although COVID-19 is linked to a prothrombotic condition, still there is no such consensus on the advantages of venous thromboembolism (VTE) prevention in an outpatient now. However, current CHEST recommendations call for anticoagulant medication to be administered to COVID-19 patients who experience proximal disseminated venous thrombosis (PDVT) or pulmonary embolism (PE) for a minimum of three months. (34)

NEUROPSYCHIATRIC

Patients should undergo psychiatric screening for common conditions such as anxiety, depression, sleeplessness, and post-traumatic stress disorder and if required, they should be referred to behavioral health professionals. Given the wide range of neurological symptoms linked to this disease, early neurology evaluation should be considered. Hemoglobin A1C (HbA1c), TSH, Thiamin, Folic acid, Vitamin B12, and Vitamin D3 must be tested in addition to the usual laboratory tests, to rule out any further contributing metabolic disorder. (35) If there are concerns about seizures or paresthesia, an EEG or EMG should be considered.

DIFFERENTIAL DIOGNOSIS

There is currently very limited information about post COVID-19 syndrome available, yet more to be explored. COVID-19 is so catastrophic that any organ system may be impacted. Therefore, post COVID-19 syndrome should be regarded as an excluding diagnosis. It is necessary to first rule out all other well-described COVID-19 problems and other acute alternative diagnosis using proper laboratory testing and imaging. The following frequently occurring conditions can be considered in the differential diagnosis of post COVID-19 syndrome. This newest clinical entity manifests various respiratory, cardiovascular, hematologic, and neuropsychiatric symptoms either alone or in combination.

DIFFERENTIAL DIAGNOSIS OF POST COVID SYNDROME

CONDITIONS	COMPLICATIONS
RESPIRATORY	Respiratory embolism, Lung fibrosis or atelectasis Bacterial pneumonia (Post Viral)
CARDIOVASCULAR	Cardiac Ischemia Myocarditis (Post Viral) Myocardial fibrosis Congestive Heart Failure, Arrhythmias
HEMATOLOGIC	Disseminated intravenous thrombosis/ coagulation (DIT / DIC)
INFECTIOUS	Bacterial (Pneumonia, Septicemia) Fungal (Mucormycosis, Aspergillosis, Cryptococcosis, Candidiasis) Reinfection & other viral infections.
NEUROPSYCHIATRIC	Cerebrovenous sinus thrombosis (CVST) Stroke Seizures Anxiety Depression Insomnia Stress Disorder (Post Traumatic)

PROGNOSIS

The prognosis of this novel clinical entity is unclear. It is most likely influenced by the intensity of the clinical symptoms, presence of other diseases, and the patient's response to treatment. To comprehend the duration and long-term implications of this new clinical entity, more clinical trials of post-COVID-19 patients are necessary.

COMPLICATIONS

The post COVID-19 syndrome is a complication of COVID-19 and related secondary infections that is becoming more widely recognized, however the additional consequences linked to this condition are still not fully understood. For a better understanding of the long-term effects of this illness, more clinical information and extensive research is needed.

PATIENT EDUCATION AND DISSUASION

Patients with this syndrome should learn the value of self-monitoring at home and, if possible, monitor periodically with the help of a home health assistant. Patients should be informed about emergency care options and encouraged to use them, when necessary, particularly when linked to neuropsychiatric manifestations. Patients should encourage seeking behavioral health counseling. Patients must be informed about the effectiveness of various vaccinations and their advantages.

IMPROVING HEALTHCARE TEAM RESULTS

Until most of the world's population receives the COVID-19 vaccine, the illness will continue to threaten global public health. COVID-19 has caused chaos around the world and has overloaded many healthcare systems. To comprehend and effectively manage this intricate and dynamic health problem, a team strategy must involve closely monitoring all COVID-19 patients throughout their recovery. A multidisciplinary and interprofessional collaborative team approach is necessary for the management of post COVID-19 syndrome. This team should include physicians from various specialties (primary care, pulmonology, cardiology, and infectious disease), physiatrists, behavioral health specialists, physical and occupational therapists, and social workers concerned with holistic health programmes. Due to the global pandemic, COVID-19 survivors require therapy that has a much greater emphasis on cardiac consequences, psychological burden, and tiredness. (36) Primary care physicians should identify this illness as early as feasible, rule out any other diagnoses that might be implicated, and, if available, refer patients to post-COVID-19 care clinics. Patients with this syndrome should learn the value of self-monitoring at home and, if possible, should regularly monitor by a home health assistant. Patients with

post COVID-19 syndrome should be promptly referred to a behavioral health specialist and, if necessary, a neurologist because this syndrome is frequently accompanied by the involvement of multiple organ systems, including neuropsychiatric abnormalities. Primary care health professionals, physicians, specialists, super specialists and mental health care professionals should work closely together to coordinate care and communicate as an interprofessional collaborative team to set up the best available treatment options for each patient. Such an interdisciplinary team approach improves patient care outcomes and decreases unneeded hospitalizations, minimizing the depletion of healthcare resources that have already been put under stress during this pandemic.

CONCLUSION

Post covid –19 syndrome has now turned into an intricate threat to the world health sector which seeks attention to its dedicated treatment and management. Increased morbidity due to post COVID-19 syndrome, impairs the quality of life. Treatment and management are well required for these Long COVID-Haulers. An interprofessional team of Clinicians, specialists, occupational therapist, social worker, self-training programme required to work and collaborate in improving and overcoming this condition. Unmanaged Long COVID-Haulers are subjected to complex morbidity and may be attributed to gross mortality. A new protocol guideline is needed to look after patients with post COVID-19 syndrome in all conceivable ways. More scientific evaluation / research is the call of time.

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