Original article

Received: Feb. 16,2022
Revised: June 2,2022
Accepted: Aug. 5, ,2022
Published: Aug 20, 2022

Medical Complications and Symptomatic Management of Post Covid Syndrome-A Review

Jophy mathew, M Sudha*, R Sambath Kumar
J.K.K. Nattraja College of Pharmacy, Namakkal (Dt), Kumarapalayam, India

Abstract

COVID-19 (multi-organ disease with a wide range of symptoms) is an ongoing pandemic, which are now extending to its long-term sequelea. The majority of patients make a recovery within 3–4 weeks of diminishing COVID-19, but a small percentage of patients continue to suffer from its persisting effects and develop sustained illness/medical problems, which can lead to long-term health issues. Fatigue, dyspnea, cough, headache, brain fog, anosmia, and dysgeusia are frequent symptoms of post-COVID-19 complications (PCS), although damage to the pulmonary, cardiovascular, cutaneous, musculoskeletal, and neuropsychiatric systems have also been observed. Patients with COVID-19 should be followed up for a long time after they have recovered, and a complete rehabilitation program can be established for them. Current scenario demands further epidemiological and clinical studies to establish the metaphors of PCS and its management. The present review aims to highlight the post COVID manifestations and management strategies as there is very limited evidence about the management of COVID-19 after the first three weeks of illness.

Key Words: COVID-19, Post covid complications, Rehabilitation program, Neuropsychiatric systems, Medical complications

Corresponding author: Sudha Muthusamy, Email: sudha.m@jkkn.ac.in

Introduction

Following an acute COVID-19 infection, a considerable number of people suffer from long-term and devastating effects. The persistent cluster of symptoms has been named as "post-COVID syndrome" by the National Institute for Health and Care Excellence (NICE). It's also known as "long-haul COVID-19," "ongoing symptomatic COVID-19," "chronic COVID-19," and "post COVID-19 syndrome."[1] This is further classified into acute post-COVID syndrome, which lasts three weeks after the primary infection, and post-COVID syndrome, which lasts longer than twelve weeks (Iqbal, F.M., et al, 2021)

COVID-19 patients should be followed up on for a long time after they have recovered, and a comprehensive rehabilitation programme can be established for them. The current scenario necessitates additional epidemiological and clinical studies to establish mechanism for PCS and its management. Because there is very little evidence about the management of COVID-19 after the first three weeks of illness, the current review aims to highlight post-COVID manifestations and management strategies.

COVID-19 has been diagnosed in approximately 117 million people worldwide as of March 2021, with more than 2.6 million deaths (Iqbal, F.M., et al, 2021). The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induces COVID-19, a heterogeneous virus that causes a wide range of symptoms, from asymptomatic to life-threatening and catastrophic disease (Salamanna,F., et al, 2021). One of the most prevalent symptoms of SARS-CoV-2 is interstitial pneumonia, which can be exacerbated by acute respiratory distress syndrome (ARDS), a disease characterized by a high death rate, particularly in elderly persons with numerous comorbidities (Mao, R., et al, 2020, Levi, M., et al, 2020).

As the COVID-19 pandemic proceeds, a slew of new symptoms have emerged such as fever, dry cough, shortness of breath, fatigue, myalgias, nausea/vomiting or diarrhea, headache, weakness, rhinorrhea, anosmia/ageusia, and many laboratory abnormalities that is lymphopenia and elevated inflammatory markers like erythrocyte sedimentation rate, C-reactive protein, ferritin, tumor necrosis factor-a, IL-1, and IL-6 have been reporte (Salamanna,F., et al, 2021, Mao, R., et al, 2020). Other significant and severe COVID-19 consequences include heart, brain, lung, liver, kidney, and coagulation system dysfunction (Long, B., et al, 2020, Mao, L., et al, 2020, Middeldorp, S., et al, 2020, Chen, Y.T., et al, 2020).

Classification of Post-COVID Syndrome

Table 1: Classifications of post-COVID syndrome. * Becker, R.C. 2021. (COVID-19 Clinic of the University of Cincinnati Medical Center)

	Type 1	Type 2	Type 3		Type 4		Type 5
Initial symptoms	Variable [a]	Mild	A Mild	B Mild	A None	B None	None
Duration of	Variable [a]	>6 weeks	3–6 months	>6 months	Variable	Variable	N/A
Period of	No	No	Yes	Yes	No	No	N/A
Delayed onset of	No	No	No		Yes ≥3 months	Yes ≥6 months	Yes

Note: Type 3A- Period of inactivity or nearly full recovery, followed by a recurrence of persistent symptoms for at least three months, Type 3B- Period of inactivity or nearly full recovery, followed by a recurrence of persistent symptoms for at least three months or at least six months, Type 4A- Asymptomatic when tests positive but get symptoms in 1 to 3 months, Type 4B- Asymptomatic when test positive but get symptoms in atleast 3 months later.

Table 1 shows that there are five categories of protracted COVID-19 syndrome, according to the University of Cincinnati Medical Center's recommended criteria for COVID-19 sequelae, depending on initial symptoms, time of onset, duration of symptoms, and period of inactivity are figured in Table 1. Type 1 comprises patients whose recovery time varies depending on the severity of the acute infection, organ problems, and underlying medical disorders, Type 2 is characterised by symptoms that last for at least six weeks from the commencement of the illness, Type 3 shows a period of inactivity or nearly full recovery, followed by a recurrence of symptoms persisting for at least three months (Type 3A) or at least six months (Type 3B), Type 4 refers to patients who are initially asymptomatic when a SARS-CoV-2 test is positive but develop symptomatic one to three months (Type 4A), or at least three months later (Type 4B), and Type 5 includes patients who are asymptomatic or have little symptoms at the time of diagnosis and may die within the next 12 months are included in this category (Becker, R.C. 2021). Amenta *et al*. from Baylor College of Medicine, Houston, classified post-acute COVID-19 manifestations in three categories, of which the first two should not be regarded as mutually exclusive. Firstly, residual symptoms that persist after recovery from acute infection. Organ dysfunction that persists after initial recovery comes the second one. Finally the new symptoms or syndromes that develop after initial asymptomatic or mild infection (Amenta, E. M., et al, 2020). Lastly, Fernandez-de-Las Penas *et al*. considered also undiagnosed cases and proposed a time-based classification as follows: potentially infection-related symptoms (up to 4–5 weeks), acute post-COVID symptoms (from week 5 to week 12), long post-COVID symptoms (from week 12 to week 24), and persistent post-COVID symptoms (lasting more than 24 weeks). Intrinsic and extrinsic predisposing factors are also considered (Fernandez-de-Las-Penas, C., et al, 2021).

Pathogenesis of post-COVID syndrome

The pathophysiology of post-COVID syndrome is not well known. Prolonged inflammation appears to play a crucial role in the aetiology of most post-COVID symptoms, according to evidence (Trougakos, I. P., et al, 2021). Alteration of neuronal functions may occur and lead to central nervous system (CNS) complications in the context of a significant rise in circulating cytokines, notably IL-6, which can pass the blood-brain barrier like altered mental status and neurocognitive disorders among others (Trougakos, I. P., et al, 2021). Furthermore, COVID-19-related inflammation may cause GABA-ergic impairment, which could be the reason of neuromotor and cognitive fatigue, as well as apathy and executive dysfunction. Indeed, animal models have revealed that an IL-6-induced hyper-inflammatory state can reduce GABA receptor density (Garcia-Oscos, F., et al., 2012).

Coronaviruses are neurotropic and may invade the blood-brain barrier and access the CNS through the use of peripheral or olfactory neurons. The hippocampus appears to be particularly susceptible to infection, that could contribute to memory loss as secondary infections (Ritchie, K., et al, 202). Wostyn hypothesised that post-COVID fatigue syndrome could be caused by damage to olfactory sensory neurons, which would result in a decreased CSF outflow through the cribriform plate and leading to the congestion of the lymphatic system with subsequent toxic build-up within the CNS (Wostyn, P, 2021). In addition, direct SARS-CoV-2 microinvasion has been hypothesised as a method that could lead to long-term neuropsychiatric problems, it appears to be less plausible given the time after infection (Amenta, E. M., et al, 2020).

Clinical manifestations

With the COVID-19 pandemic raging around the world, many recovered patients are still suffering from the infection's persistent effects, which include respiratory, cardiac, haematological, neuropsychiatric, renal, endocrine, cutaneous, gastrointestinal and hepatobiliary. The most common manifestation of Long-COVID-19 is the persistence of the physical symptoms seen in acute viral illness (Nalbandian, A., et al, 2020).

Pulmonary

• Dyspnea, decreased exercise capacity and hypoxia are commonly persistent symptoms and signs (Nalbandian, A., et al, 2020).
• Follow-up of COVID-19 survivors revealed reduced diffusion capacity, restricted pulmonary physiology, ground-glass opacities, and fibrotic alterations on imaging (Nalbandian, A., et al, 2020).
• As clinically relevant, home pulse oximetry, 6MWTs, PFTs, high-resolution computed tomography of the chest, and computed tomography pulmonary angiography may be used to monitor the progression or recovery of pulmonary disease and function (Nalbandian, A., et al, 2020).

Hematologic

• Thromboembolic events (venous thromboembolism, egmental pulmonary embolism, intracardiac thrombus, thrombosed arteriovenous fistula and ischemic stroke) have been noted to be <5% in post-acute COVID-19 in retrospective studies (Nalbandian, A., et al, 2020).
• The duration of the hyperinflammatory state induced by infection with SARS-CoV-2 is unknown (Nalbandian, A., et al, 2020).
• In patients with predisposing risk factors for immobility, persistently elevated d-dimer levels (greater than twice the upper limit of normal), and other high-risk comorbidities such as cancer, direct oral anticoagulants and low-molecular-weight heparin may be considered for extended thromboprophylaxis after a risk–benefit discussion (Nalbandian, A., et al, 2020).

Cardiovascular

• Persistent symptoms may include palpitations, dyspnea and chest pain (Nalbandian, A., et al, 2020).
• Increased cardiometabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI), arrhythmias, tachycardia, and autonomic dysfunction are all possible long-term consequences (Nalbandian, A., et al, 2020).
• Serial clinical, echocardiography, and ECG follow-up may be used to examine patients with cardiovascular issues during an acute infection or those who have chronic heart symptoms (Nalbandian, A., et al, 2020).

Neuropsychiatric

• Persistent abnormalities may include fatigue, myalgia, headache, dysautonomia and cognitive impairment (brain fog) (Nalbandian, A., et al, 2020).
• Anxiety, depression, sleep disturbances and PTSD have been reported in 30–40% of COVID-19 survivors, similar to survivors of other pathogenic coronaviruses (Nalbandian, A., et al, 2020).
• Immune dysregulation, inflammation, microvascular thrombosis, iatrogenic medication effects, and psychosocial effects of infection are all part of the pathophysiology of neuropsychiatric complications (Nalbandian, A., et al, 2020).

Renal

• The majority of individuals with acute COVID-19 achieve resolution of AKI; nevertheless, at 6 months follow-up, decreased eGFR has been documented (Nalbandian, A., et al, 2020).
• COVID-19 associated nephropathy (COVAN) may be the predominant pattern of renal injury in individuals of African descent (Nalbandian, A., et al, 2020).
• Early and diligent follow-up in AKI survivor clinics may assist COVID-19 survivors with persistently compromised renal function (Nalbandian, A., et al, 2020).

Endocrine

• Endocrine complications include new or worsened diabetes mellitus control, subacute thyroiditis, and bone demineralization (Nalbandian, A., et al, 2020).
• Patients with newly diagnosed diabetes who do not have established risk factors for type 2 diabetes, hypothalamic–pituitary–adrenal axis suppression, or hyperthyroidism should have adequate laboratory tests and be sent to endocrinology (Nalbandian, A., et al, 2020).

Gastrointestinal and hepatobiliary

• Prolonged viral fecal shedding can occur in COVID-19 even after negative nasopharyngeal swab testing (Nalbandian, A., et al, 2020).
• COVID-19 has the potential to modify the gut microbiome, including opportunistic microbe enrichment and commensal depletion (Nalbandian, A., et al, 2020).

Dermatologic

• Hair loss is the predominant symptom and has been reported in approximately 20% of COVID-19 survivors (Nalbandian, A., et al, 2020).

Multisystem inflammatory syndrome in children (MIS-C)

• Diagnostic criteria includes <21 years old with fever, elevated inflammatory markers, multiple organ dysfunction, current or recent SARS-CoV-2 infection and exclusion of other plausible diagnoses (Nalbandian, A., et al, 2020).
• Typically affects children >7 years and disproportionately of African, Afro-Caribbean or Hispanic origin (Nalbandian, A., et al, 2020).
• Cardiovascular (coronary artery aneurysm) and neurologic (headache, encephalopathy, stroke and seizure) complications can occur (Nalbandian, A., et al, 2020).

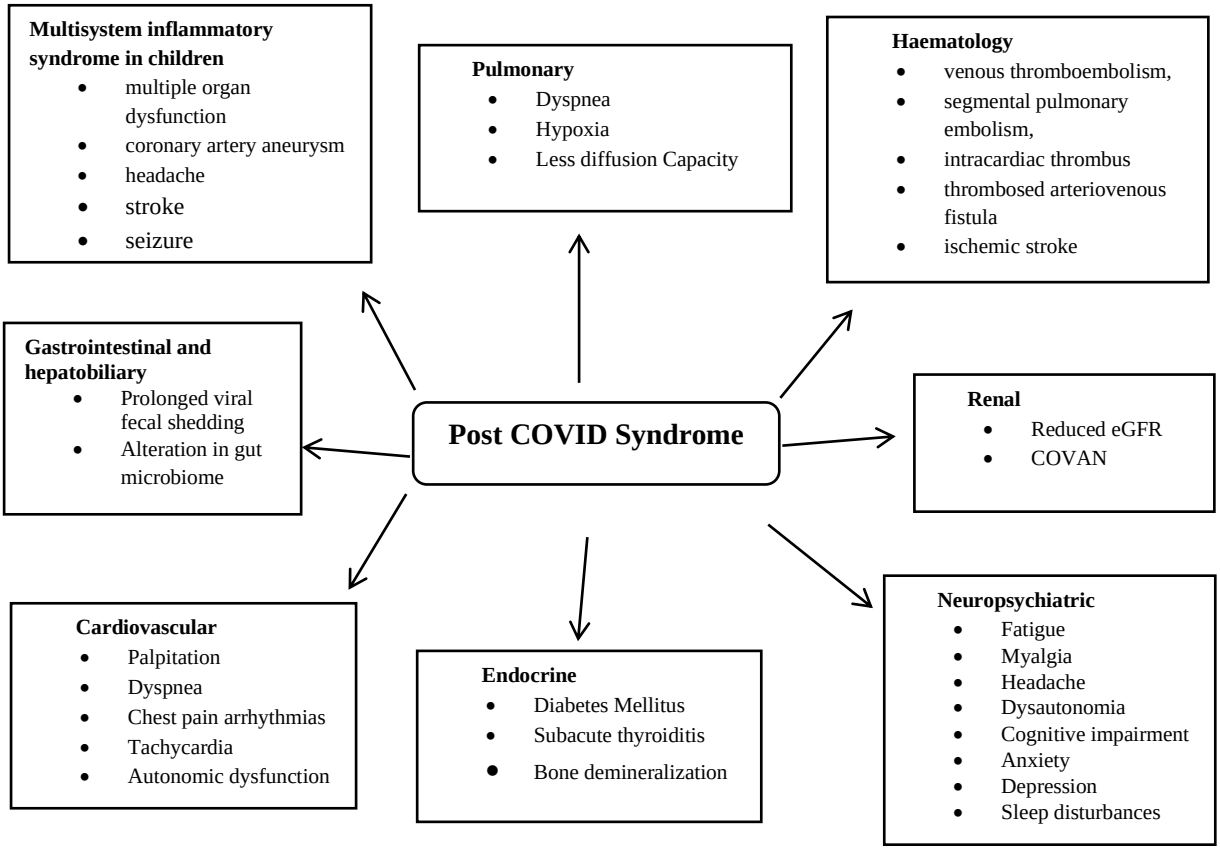

Figure:1 Clinical presentation of post COVID syndrome

Note: The COVID-19 pandemic raging around the world, many recovered patients are still suffering from the infection's persistent effects, which include respiratory, cardiac, haematological, neuropsychiatric, renal, endocrine, cutaneous, gastrointestinal and hepatobiliary. The most common manifestation of Long-COVID-19 is the persistence of the physical symptoms seen in acute viral illness.

Chronic complications

The chronic complications that may persist after infection with SARS-CoV-2 mainly affect the respiratory, cardiovascular, renal and neurological systems. In June 2020, one of the first studies to look into the long-term effects of COVID-19 on the respiratory system was released. A total of 57 patients were followed up, they had a pulmonary function test, a six-minute walk test, and chest computed tomography (CT) scan 30 days after being discharged from the hospital. Tomographic alterations were seen in 31 patients (54.3%), abnormalities in pulmonary function tests were detected in 43 patients (75.4%). Patients with severe disease exhibited a greater incidence of impairment of diffusing capacity of the lungs for carbon monoxide (DLCO) (75.6 percent versus 42.5 percent; P = 0.019) when compared to non-severe cases. More than half of the COVID-19 patients in the early stages of recovery had reduced DLCO, lower respiratory muscle strength, and abnormalities on pulmonary imaging (Huang, Y., et al, 2020). These data were not completely documented by Lerum *et al*. who published a prospective study on 103 COVID-19 patients, including 15 cases that were considered severe and were treated in an IC U (Lerum, T.V., et al, 2021). Their

aim was to report patient's quality of life, state of dyspnea, pulmonary function and chest CT findings, three months after their discharge from hospital. They found that on chest CT scan, a 1/4th of their patients had opacities and had decreased diffusion capacity. However, in their sample, this was not reflected in increased dyspnea or impaired pulmonary function. The presence of pathological CT findings was most intimately associated to ICU admission.

Cardiac abnormalities have also been studied. Cardiovascular magnetic resonance imaging (MRI) was performed on average 71 days after the disease was diagnosed in a cohort study of 100 patients who had recovered from COVID-19. Cardiac abnormalities were discovered in 78 patients, with active myocardial inflammation in 60 patients. This occurred regardless of the patient's pre-existing conditions, disease severity, general evolution of the acute disease, or time since the initial diagnosis (Puntmann, V.O., et al, 2020). Nonetheless, the long-term evolution of such cases remains uncertain. Rajpal *et al.* also used cardiac MRI but studied a very specific population. They recruited 26 university athletes with COVID-19, in the outpatient department (Rajpal, S., et al, 2020). Through transthoracic echocardiograms and cardiac MRI, none of them were found to have any ST/T wave alterations in electrocardiograms, and all of them had ventricular volumes and functions that were within the normal range. None of the athletes presented elevated serum levels of troponin I. Four of them (15%) had cardiac MRI findings consistent with myocarditis. The neurological alteration that has been most reported after COVID-19 is persistence of olfactory dysfunction. Otte *et al*. analyzed the sense of smell of 50 consecutive patients, at least three weeks after they had recovered from an acute condition (Otte, M.S., et al, 2020). During the course of the disease, 94 percent of these patients reported that they had suddenly lost their sense of smell. When the patients were given an olfactory test after their recovery, 38 percent still had a deficiency, while 61.7% had completely recovered their sense of smell. These include changes in cognition and memory, as well as sleep deregulation. Some psychiatric changes, such as mood changes associated with depression or anxiety, have also been reported. Other consequences, albeit hypothetical, may also impact the post-COVID-19 population. According to a study published in the journal Future Oncology, infection with SARS-CoV-2 may have a carcinogenic effect, particularly in the pulmonary tissue that could lead to an increased risk of cancer in these patients in the future (Hays, P. 2020). What to expect from these chronic changes, and even how to treat them, is unknown. SARS-CoV-2 causes chronic modifications to the lungs, kidneys, heart, and endothelium.

Management

Treatment methods for post-COVID sequelae will differ significantly based on the clinical profile and demands of each patient. Prior pre-existing medical conditions should be considered in management strategies, and care teams should provide regular follow-up for each patient until symptoms subside and for some time afterwards (Oronsky, B., et al, 2021). Post-hospital discharge care of COVID-19 survivors has been recognized as a major priority research by professional organizations (Bai, C. 2020), and treatment guidelines for these patients are still being developed (Shah, W., et al, 2021). Although home pulse oximetry using Food and Drug Administration-approved devices has been proposed as a useful tool for monitoring patients with persistent symptoms, supporting evidence is currently lacking (Luks, A.M., et al., 2020, Brigham, E. 2021).

A preliminary observation of significant symptomatic and radiological improvement in a small UK cohort of COVID- 19 survivors with organising pneumonia 6 weeks after hospital discharge suggests that corticosteroid treatment may

be beneficial in a subset of patients with post-COVID inflammatory lung disease (Myall, K.J. 2021). In the post-acute COVID-19 Chinese study, steroid use during acute COVID-19 was not associated with diffusion impairment or radiographic abnormalities at 6 months follow-up (Huang, C. 2021). Lung transplantation has previously been performed for fibroproliferative lung disease after Acute Respiratory Distress Syndrome (ARDS) (Chang, Y. 2018) due to influenza A (H1N1) infection and COVID-19 (Bharat, A. 2020, Chen, J. 2020). Antifibrotic therapies are being tested in clinical trials to prevent pulmonary fibrosis after COVID-19 (George, P.M., et al, 2020).

Hematologic treatment

Direct oral anticoagulants and low-molecular-weight heparin are preferred anticoagulation agents over vitamin K antagonists because they do not require frequent monitoring of therapeutic levels and have a lower risk of drug–drug interactions (Bikdeli, B. 2020, Barnes, G.D. 2020). Similar to provoked Venous Thrombo Embolism (VTE), therapeutic anticoagulation is recommended for ≥ 3 months for those with imaging-confirmed VTE (Bai, C. 2020, Moores, L.K. 2020).

Cardiovascular treatment

In those with cardiovascular consequences during an acute infection or persistent cardiac symptoms, serial clinical and imaging examination with ECG and echocardiography at 4–12 weeks may be recommended (Bikdeli, B. 2020, Desai, A.D., et al, 2020). Despite initial concerns about elevated ACE2 levels and the potential of acute COVID-19 when using Renin-Angiotensin-Aldosterone System (RAAS) inhibitors, they have been proved to be safe and should be continued in patients with stable cardiovascular disease (Bozkurt, B., et al, 2020, Lopes, R.D., et al, 2020). Instead, abruptly stopping RAAS inhibitors could be dangerous (Vaduganathan, M., et al, 2020).

Neuropsychiatric treatment

For neurologic problems such as headaches, standard therapy should be used, with imaging examination and referral to a specialist reserved for refractory headache (Guzik, T.J., et al, 2020). In individuals with cognitive impairment, a second neuropsychological evaluation should be considered in the post-acute illness situation.

Renal treatment

While the risk of dialysis-dependent AKI at discharge is low, the amount of renal function recovery needs to be evaluated. As a result, COVID-19 survivors with persistently reduced renal function in the post-acute infection phase may benefit from early and close follow-up with a nephrologist in AKI survivor clinics, which has been linked to better outcomes in the past (Do, T.P., et al, 2019, Kaseda, E.T, et al, 2020).

Endocrine treatment

In patients with newly diagnosed diabetes mellitus who may not have traditional risk factors for type 2 diabetes, serologic testing for type 1 diabetes associated autoantibodies and repeat post-prandial C-peptide measurements should be obtained at follow-up, whereas it is reasonable to treat patients with such risk factors as if they had ketosis-prone type 2 diabetes (Meier, P., et al, 2011). Corticosteroids can be used to treat hyperthyroidism caused by SARS-CoV-2 related destructive thyroiditis, although new-onset Graves' disease should also be ruled out (Ruggeri, R.M., et al, 2020).

Gastrointestinal and hepatobiliary treatment

COVID-19 has the potential to transform the gut microbiota, favouring opportunistic infectious microbes and reducing beneficial commensals (Donati Zeppa, S., et al, 2020, Bradley, K.C., et al, 2021). The gut microbiota's ability to influence the course of respiratory infections (the gut–lung axis) has previously been observed in influenza and other respiratory illnesses (Miquel, S., et al, 2020).

Dermatologic treatment

In the post-acute COVID-19 Chinese trial, only 3% of patients had a skin rash after 6 months (Chang, Y. 2018). Hair loss was the most common dermatologic complaint, with almost 20% of individuals diagnosed it (Chang, Y. 2018, Garrigues, E., et al, 2020). Hair loss could be triggered by telogen effluvium, which is characterized by a viral infection or a stress response (Chang, Y. 2018).

Conclusion

COVID-19 is the current illness garnering the most attention among medical providers. Its post-discharge symptoms are yet to be investigated but they pose a major socio–economic and clinical challenge. From the recent reports, the most common symptoms of post Covid-19 syndrome includes dyspnoea, fatigue, thromboembolic events, myalgia, headache, anxiety, depression and sleep disturbances. Corticosteroids, antifibrotics, anticoagulants and certain antihypertensives were the main stays of PCS management. Patients with COVID-19 should be on long term follow up and observation even after recovery and a comprehensive rehabilitation program can also be implemented for such patients. The current scenario demands further epidemiological and clinical studies to establish the mechanisms of PCS and its management.

Acknowledgemen

With immense pleasure, I would like express my heartful appreciation to our respected guide Sudha Muthusamy, M. Pharm, Assistant Professor Department of Pharmacology for her remarkable supervision, incredible support and valuable suggetions. I extend my sincere thanks to our esteemed Principal Dr.R.Sambath Kumar, M.Pharm., Ph.D., Professor and Head, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam for his inspiration. I offer my respectful regards to the founder (Late) Thiru J.K.K.Nattraja Chettiar, for providing us with this historical institution.

References

Iqbal, F.M., Lam, K., Sounderajah, V., Clarke, J.M., Ashrafian, H., Darzi, A. (2021). Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine*, 36:100899.

Salamanna, F., Veronesi, F., Martini. L, Landini, M.P., Fini, M. (2021). Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data. *Front.Med. (Lausanne)*, 8:653516.

Mao, R., Qiu, Y., He, J.S., et al. (2020). Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*, 5(7):667-678.

Levi, M., Thachil, J., Iba, T., Levy, J.H. (2020). Coagulation abnormalities and thrombosis in patients with COVID-19. *Haematol*, 7(6):e438-e440.

Long, B., Brady, W.J., Koyfman, A., Gottlieb, M. (2020). Cardiovascular complications in COVID-19. *Am J Emerg Med*, 38(7):1504-1507.

Mao, L., Jin, H., Wang, M., et al. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *Neurol*, 77(6):683-690.

Middeldorp, S., Coppens, M., Van Haaps, T.F., et al. (2020). Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*, 18(8):1995-2002.

Chen, Y.T., Shao, S.C., Hsu, C.K., Wu, I.W., Hung, M.J., Chen, Y.C. (2020) Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. *Crit Care*, 24(1):346.

Becker, R.C. (2021). COVID-19 and its sequelae: a platform for optimal patient care, discovery and training.. *J Thromb Thrombolysis*, 51(3):587-594.

Amenta, E.M., Spallone, A., Rodriguez-Barradas, M.C., El Sahly, H.M., Atmar, R.L., Kulkarni, P.A. (2020). Postacute COVID-19: An Overview and Approach to Classification. *Open Forum Infect Dis*, 7(12):509.

Fernández-de-Las-Peñas, C., Palacios-Ceña, D., Gómez-Mayordomo, V., Cuadrado, M.L., Florencio, L.L. (2021). Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. *Int J Environ Res Public Health*, 18(5):2621.

Trougakos, I.P., Stamatelopoulos, K., Terpos, E., et al. (2021). Insights to SARS-CoV-2 life cycle, pathophysiology, and rationalized treatments that target COVID-19 clinical complications. *J Biomed Sci*, 28(1):9.

Garcia-Oscos, F., Salgado, H., Hall, S., et al. (2012). The stress-induced cytokine interleukin-6 decreases the inhibition/excitation ratio in the rat temporal cortex via trans-signaling. *Biol Psychiatry*, 71(7):574-82.

Ritchie, K., Chan, D., Watermeyer, T. (2020). The cognitive consequences of the COVID-19 epidemic: collateral damage?. *Brain Commun*, 2(2):069.

Wostyn, P. (2021). COVID-19 and chronic fatigue syndrome: Is the worst yet to come?. *Med Hypotheses*, 146:110469.

Nalbandian, A., Sehgal, K., Gupta, A., et al. (2020). Post-acute COVID-19 Syndrome. *Nat. Med*, 27:601-15.

Huang, Y., Tan, C., Wu, J., et al. (2020). Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*, 21(1):163.

Lerum, T.V., Aaløkken, T.M., Bronstad, E., et al. (2021). Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J*, 57(4):2003448.

Puntmann, V.O., Carerj, M.L., Wieters, I., et al. (2020). Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*, 5(11):1265-73.

Rajpal, S., Tong, M.S., Borchers, J., et al. (2020). Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. *JAMA Cardiol*, 6(1):116-8.

Otte, M.S., Klussmann, J.P., Luers, J.C. (2020). Persisting olfactory dysfunction in patients after recovering from COVID-19. *J Infect*, 81(3):58.

Hays, P. (2020). Clinical sequelae of the novel coronavirus: does COVID-19 infection predispose patients to cancer?. *Future Oncol*, 16(20):1463-74.

Oronsky, B., Larson, C., Hammond, R.C., Oronsky, A., Kesari, S., Lybeck, M. (2021). A Review of persistent post-COVID syndrome (PPCS). *Clin. Rev Allergy Immunol*, 20;1-9.

Bai, C. (2020). Updated guidance on the management of COVID-19: from an American Thoracic Society/European Respiratory Society coordinated International Task Force. *Eur Respir Rev*, 29:200287.

Shah, W., Hillman, T., Playford, E.D., Hishmeh, L. (2021). Managing the long term effects of COVID-19: summary of NICE, SIGN, and RCGP rapid guideline. *Brit. Med. J*, 372:136.

Luks, A.M., Swenson, E.R. (2020). Pulse oximetry for monitoring patients with COVID-19 at home. Potential pitfalls and practical guidance. *Ann. Am. Thorac. Soc*, 17:1040–46.

Brigham, E. (2021). The Johns Hopkins Post-Acute COVID-19 Team (PACT): a multidisciplinary, collaborative, ambulatory framework supporting COVID-19 survivors. *Am. J. Med*, 12:9.

Myall, K.J. (2021). Persistent post-COVID-19 inflammatory interstitial lung disease: an observational study of corticosteroid treatment. *Ann Am Thorac* Soc, 18(5): 799–806.

Huang, C. (2021). 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*, 397:220–32.

Chang, Y. (2018). Lung transplantation as a therapeutic option in acute respiratory distress syndrome. *Transplantation*, 102:829–837.

Bharat, A. (2020). Lung transplantation for patients with severe COVID-19. *Sci Transl* Med, 12:4282.

Chen, J. (2020). Lung transplantation for an ARDS patient post-COVID-19 infection. *Chest*, 157:453.

George, P.M., Wells, A.U., Jenkins, R.G. (2020). Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med*, 8:807–15.

Bikdeli, B. (2020). COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol*, 75:2950–73.

Barnes, G.D. (2020). Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*, 50:72–81.

Moores, L.K. (2020). Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST Guideline and Expert Panel report. *Chest*, 158:1143–63.

Bikdeli, B. (2020). Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. *Thromb Haemost*, 120:1004–24.

Desai, A.D., Boursiquot, B.C., Melki, L., Wan, E.Y. (2020). Management of arrhythmias associated with COVID-19. *Curr. Cardiol. Rep*, 23:2.

Bozkurt, B., Kovacs, R., Harrington, B. (2020). Joint HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. *J Card Fail*, 26:370.

Lopes, R.D., Macedo, S.V., Pedro, G.M., et al. (2021). Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *J Am Med Assoc*, 325:254–64.

Vaduganathan, M., Vardeny, O., Micheal, T., McMurray, J.V., Pfeffer, A.M., Solomon, S.D. (2020). Renin–angiotensin–aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*, 382:1653–59.

Guzik, T.J., Mohiddin, A.S., Dimarco, A., et al. (2020). COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*, 116:1666–87.

Do, T.P., Remmers, A., Schytz, H.W., et al. (2019). Red and orange flags for secondary headaches in clinical practice: SNNOOP10 list. *Neurology*, 92:134–44.

Kaseda, E.T, Levine, A.J. (2020). Post-traumatic stress disorder: a differential diagnostic consideration for COVID-19 survivors. *Clin Neuropsychol*, 34:1498–1514.

Meier, P., Bonfils, R.M., Vogt, B., Burnand, B., Burnier, M. (2011). Referral patterns and outcomes in noncritically ill patients with hospital-acquired acute kidney injury. *Clin. J. Am. Soc. Nephrol*, 6:2215–25.

Ruggeri, R.M., Campenni, A., Siracusa, M., Frazzetto, G., Gullo, D. (2020). Subacute thyroiditis in a patient infected with SARS-COV-2: an endocrine complication linked to the COVID-19 pandemic. *Hormones (Athens)*, 20:219–21.

Donati Zeppa, S., Agostini, D., Piccoli, G., Stocchi, V., Sestili, P. (2020). Gut microbiota status in COVID-19: an unrecognized player? *Front Cell Infect Microbiol*, 10:576551.

Bradley, K.C., Finsterbustch, K., Schnepf, D., Crota, S., Liorian. M., Davidson, S., et al. (2021). Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. *Cell Rep*, 28:245–56.

Miquel, S., Martin, R., Rossi, O., Bermudez-Humaran, L.G., Chatel, J.M., Sokol. H., et al. (2020). *Faecalibacterium prausnitzii* and human intestinal health. *Curr Opin Microbiol*, 16:255–61.

Garrigues, E., Janvier, P., Kherabi, Y., et al. (2020). Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*, 81:4–6.