

## The “Long - COVID 19”: How do we address this alarming situation?

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The global COVID-19 pandemic began in Wuhan, China, in Dec 2019 and has caused more than 464 million infections and 6 million deaths, reported to WHO as of March 18, 2022. India has reported more than 43 million confirmed cases of COVID19, including 516281 deaths [1]. This is a third novel virus belonging to the large family “coronavirus” similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). All viruses, including SARS-CoV-2, the virus that causes COVID-19, mutate over time. So far hundreds of variations of this virus have been identified worldwide and are being continuously monitored closely since Jan 2020 for their phenotypic characteristics such as transmissibility, disease severity, risk of reinfection, and impacts on diagnostics and vaccine performance which are of global public health significance. Currently circulating variants of concern (VOC) include Delta (India, May 2021), and Omicron (multiple countries, Nov 2021) variants. Previously circulating VOCs reported are Alpha (United Kingdom, Dec 2020), Beta (South Africa, Dec 2020), and Gamma (Brazil, Jan 2021). Other circulating variant of interest (VOI) and their geographical area of first identification as per WHO, include epsilon (USA), zeta (Brazil), eta (Multiple countries), theta (Philippines), Iota (USA), kappa (India), lambda (Peru) and mu (Colombia) [1].

Safe and effective vaccines for COVID-19 have now halted the devastating impact of this infection in not just disease transmissibility but also disease outcomes. Globally, as of 17 March 2022, a total of 10.99 billion vaccine doses have been administered [1]. Around 64% of the world population has received at least one dose of a COVID19 vaccine. In India, more than 819 million people have been fully vaccinated and around 20 million have taken precaution dose of COVID19 [2]. Currently authorized vaccines offer relatively less protection against infection due to Omicron compared to initial strains even though residual benefits are still substantial. Hence policy administrators must try to increase uptake of primary vaccination and boosters in all eligible populations.

As the COVID-19 pandemic has progressed worldwide, evidence has emerged that some survivors with COVID19 infection who recovered from acute illness and discharged from hospital are experiencing prolonged medical, neuro-

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psychological, and socio-economic consequences, that result in loss of disability adjusted life years (DALYs)[3-8]. Given the varied clinical features and severity of COVID19 infection, there is a critical need to understand the emerging notion of long-term health consequences arising from this pandemic. Thus, with better primary prevention options and therapeutics, the focus of medical care is now shifting to addressing the challenge of the “post COVID phase”. Post COVID syndrome is an umbrella term that is synonymous with long haulers, long COVID19, post-acute sequelae of COVID19, chronic COVID, long COVID19 syndrome, post-acute COVID19, and late sequelae. Recently published guideline by National Institute for Health and Care Excellence (NICE) has provided clinical case definitions of the effects of COVID19 infection at different times [9]. The investigators acknowledged that new, ongoing, or recurring symptoms 12 weeks or more from acute illness onset might be more indicative of post-COVID-19 syndrome. The term “Long-COVID” includes both ongoing symptoms and post COVID syndrome that continue or develop after acute COVID19

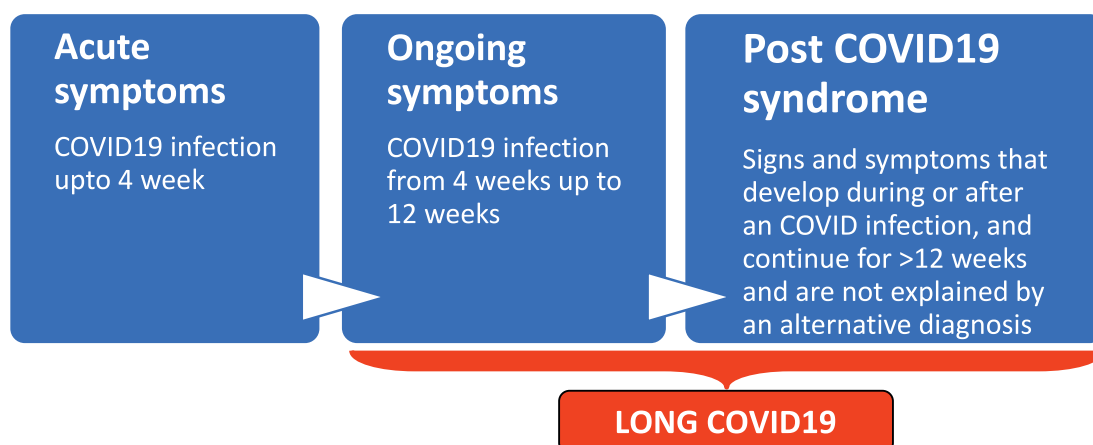


Figure 1: Clinical case definitions of the effects of COVID19 infection at different times. (Source NICE guideline [9])

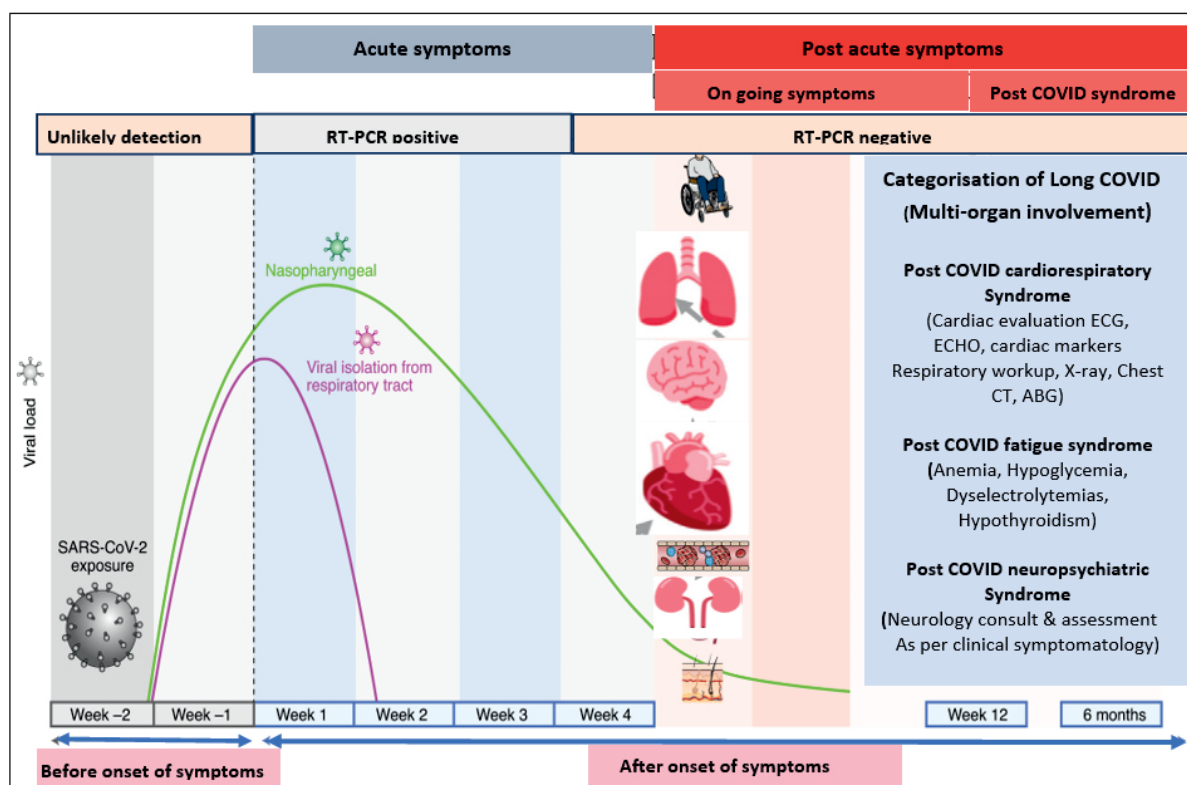


Figure 2: Approach to patients with long COVID19

infection (fig. 1).

Clinical symptoms of this new syndrome are highly variable and can affect multiple dimensions including physical, mental, and social wellbeing [3-5]. There is no consensus on the disease phenotype. However, the most common pattern is the persistence of initial symptoms (but are not limited to) like fatigue, coughing, dyspnoea, abdomen pain, diarrhoea, chest pain, arthralgia, and myalgia [10]. There is a frequent overlay with neuropsychiatric disorders such as depression, anxiety, insomnia, headache, and ‘brain fog’ or cognitive

disorders and palpitations [10]. The exact frequency of these non-specific symptoms in this evolving syndrome is not yet available. Chronic complications that seen following acute infection with COVID19 affect mainly the pulmonary, cardiovascular, oropharynx, ocular, hematologic, autoimmune, and neuropsychological systems but sometimes they may involve the endocrine, gastrointestinal, and renal systems (Table 1). Common risk factors for this syndrome include pre-existing respiratory disease, hospitalization during acute infection, obesity, ages 40-49 years, dyspnoea at 4-8 weeks follow-up, women, co-

**Table 1: Multi-organ involvement and its pathogenesis, clinical findings and management in long COVID19 infection.**

System	Pathophysiology involved in long COVID infection	Clinical manifestations	Management recommendations
<b>Cardiovascular</b>	Immune-mediated myocardial and microvascular destruction. a). myositis, b). Dysfunction of the afferent autonomic nervous system c). fibrosis, d) Fibrotic changes are accompanied by an increase in cardiac fibromyoblasts	Chest tightness Chest pain, palpitations, pericarditis, myocarditis, fibrosis, arrhythmias/death	Initial assessment with non-invasive technology (ECG, ECHO, CRP, Trop-T) and escalate to invasive testing and referral in case of abnormality at the initial evaluation
<b>Pulmonary</b>	Viral mediated parenchyma damage; immune mediated microvascular dysfunction a). production of proinflammatory cytokines and ROS b). endothelial damage triggers the activation of fibroblast c). development of prolonged hyperinflammatory and hypercoagulable state	Dyspnea, hypoxia, fatigue, ground glass opacities and pulmonary fibrosis	Initial evaluation through virtual/in-person follow-up at 4-6 weeks and at 12 weeks post discharge Dyspnea – Pulmonary and cardiac workup, follow-up with PFT, 6MWT, chest X-ray, PE work-up, ECHO, and HRCT chest if indicated
<b>Integumentary</b>	Immune-mediated microvascular dysfunction; stress	Hair loss, skin rash, urticarial lesions, angioedema	Refer to specialist as necessary.
<b>Haematology</b>	Immune mediated endothelial dysfunction	Venous, arterial, pulmonary thromboembolisms	Consider extended high-risk survivors based on shared decision making. Thromboprophylaxis, workup for PE <i>Hospitalized patients:</i> CBC, PT and aPTT, fibrinogen and D-Dimer <i>Outpatient</i> (symptomatic or at risk): same as in-patient Escalate to invasive testing and imaging studies.
<b>Neuropsychiatric</b>	Immune-mediated damage a). Glial cells activation by long term immune response. b). Hyperinflammatory and hypercoagulable states. c). BBB damage and dysregulation. d). autonomic dysfunction. e). cognitive impairment.	Psychological (anxiety, depression, sleep disorder, PTSD, low mood, reduce QoL) Neuro-cognitive (memory impairment, confusion, concentration impairment) and peripheral nerve pathologies	Neuropsychiatric assessment, and validated screening tools to be used for evaluation of depression, anxiety, OCD, sleep disturbances, PTSD and cognitive impairments. Detailed evaluation and counselling, lifestyle changes. Standard therapies with referral to neurological specialists for refractory conditions or imaging abnormalities.
<b>Endocrine</b>	Viral mediated insulin decreases and resistance; immune-mediated endocrine parenchymal destruction	New-onset diabetes, worsening pre-existing diabetes, DKA, subacute thyroiditis, graves thyrotoxicosis	Initial assessment for newly detected diabetes (testing for antibody to beta cells) and rule out risk factors for diabetes. Investigations to rule out new onset thyroid autoimmune disease, thyroiditis.
<b>Gastrointestinal symptoms</b>	Viral mediated alterations in fecal microbiota	Loss of appetite, nausea, acid reflux, diarrhoea, abdominal distension, belching, vomiting	Refer to gastrointestinal specialist as necessary.
<b>Renal</b>	Viral mediated parenchyma damage; immune mediated microvascular damage	AKI, glomerular and tubular diseases	Early referral with nephrology clinic after discharge for patients with COVID19-AKI

6MWT; Six-minute walk testing, OCD; Obsessive compulsive disorder, BBB; Blood-brain barrier, DKA; Diabetic ketoacidosis, PE; Pulmonary embolism

morbidities such as hypertension, diabetes, obesity, kidney disease, cardiovascular disease, cancer, and organ transplant patients [11,12]. Additionally, those who had more than 5 symptoms in acute stage of illness are likely to get long COVID syndrome [11,12]. Pathogenic mechanisms for this novel disease complex is also varied with autoreactive antibodies, adverse effects of drugs used for treatment, complication related to COVID effects, the superadded impact of comorbidities, sequelae of organ damage, inflammatory and metabolic changes during initial infection, persistent of chronic inflammation, adverse impact of intrahospital interventions, post intensive care syndrome and, very rarely, the persistence of virus in the body [12]. A wide range of central, peripheral, and psychological/social factors may contribute post COVID fatigue syndrome.

Identification and evaluation of persistent post-COVID sequelae is possible using a holistic, patient-centred approach that starts with comprehensive clinical history (that includes the nature, and severity of previous/ongoing symptoms as well as recognition of cognitive and psychological symptoms), thorough physical examination, serial assessments of functional status, and quality-of-life parameters. This may also include doing appropriate laboratory investigations (full blood count, biochemistry panel, c-reactive protein, exercise tolerance test, swab RT-PCR and/or antibody testing), CT/radiologic imaging (12 weeks after acute infection). Following clinical assessment, treatment is initiated based on the principles of shared decision-making, multidisciplinary intervention which also involves individualized rehabilitation services and self-management strategies (Table 1). It is necessary to follow relevant national or international guidelines on referral of people with substantial cognitive dysfunction, anxiety, depression, or other psychiatric symptoms to specialists.

In this issue of the journal, Budhiraja et al, from India provide key insights on this time-relevant topic [13]. The authors conducted a multicentric, observational follow-up study that aimed to describe long-term health consequences of COVID19 infection with a follow-up period extending to 12 months in a cohort of hospitalized patients with acute manifestations of COVID-19 infection who survived unto discharge. It is interesting to note that out of 990 respondents, as much as 40% of patients had long-COVID syndrome. There was no correlation to age, gender, comorbidities, or disease severity at presentation. All patients reported minor symptoms such as fatigue, myalgia, neuro-psychiatric symptoms like depression, anxiety, “brain fog” and sleep disorder and persistence of breathlessness. Some of the drawbacks of the study included the absence of face-to-face conversation which limited the possibility of objective assessment of clinical syndrome while also introducing subjective bias. There was substantial attrition rate before second follow-up

limiting our understanding on the temporal patterns if these symptoms. It is hoped that similar studies in different communities will help to identify geographical difference of disease presentation and allow better understanding of this new disease entity.

In conclusion, early data on “long COVID-19 syndrome” indicates a high percentage of convalesced COVID-19 patients with distressing persistent and long-term symptomatology including young adults who have few comorbidities. A multimodality and multidisciplinary disciplinary approach is needed to effectively deal with this emerging sequelae of the receding COVID-19 pandemic.

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