


Emerging spectrum of post-COVID-19 syndrome

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ABSTRACT

'Post-COVID-19 syndrome' refers to symptoms in the convalescent phase following initial COVID-19 infection. This term encompasses a wide array of presentation involving lungs, heart and the neuromuscular system. Pulmonary manifestations include post-COVID-19 fibrosis, which is akin to post acute respiratory distress syndrome fibrosis and may reflect the permanent damage to the lungs following an initial bout of infection. Cardiovascular system is often involved, and the presentation can be in terms of acute coronary syndrome, myocarditis and heart failure. Clinical manifestations are often varied and non-specific, which entails a detailed workup and a multidisciplinary approach. Post-COVID-19 syndrome adds to the overall disease morbidity and leads to a prolonged hospital stay, greater healthcare utilisation and loss of productivity marring the country's dwindling economy. Thus, it is imperative that post-COVID-19 syndrome be prevented and identified early followed by a prompt treatment.

INTRODUCTION

COVID-19 has emerged as a pandemic with a substantial impact on the global population.¹ This emerging disease entity is caused by a novel coronavirus SARS-CoV-2, which is homologous to the other coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). It often manifests as an acute respiratory illness; however, it can have a multisystem involvement with far-reaching consequences. In the majority of cases, disease course is uneventful leading to recovery from the initial bout of infection.¹ However, a proportion of patients can develop a constellation of signs and symptoms in the convalescent phase of the disease process often as a sequelae to the initial infection, an entity that can be termed as 'post-COVID-19 syndrome'.² Though the standardised definitions for this entity are lacking, recently, Greenhalgh *et al*³ defined 'post-acute COVID-19' as symptoms that have extended beyond 3 weeks of the onset of illness and 'chronic COVID-19' as symptoms extending beyond 12 weeks of onset of illness. However, the definition is non-specific, and the authors suggested that a COVID-19 positivity is not mandatory. Evidence from the previous severe acute respiratory syndrome (SARS) pandemic has shown that symptoms can persist even after complete recovery from the initial bout of infection. This entity, which was termed 'chronic post-SARS syndrome', referred to a constellation of symptoms of 'chronic fatigue,

diffuse myalgia, pain, weakness, depression and sleep disturbance'.⁴ In a study among SARS survivors, more than 40% of patients had active psychiatric illnesses, while 40.3% documented chronic fatigue of whom 27.1% met the modified 1994 Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome. In these patients, psychiatric symptoms and chronic fatigue did persist among the survivors even at 4 years of follow-up.⁵ Similarly, persistent respiratory and cardiac symptoms were observed in these patients as well as those recovering from MERS infection.^{6–8}

EPIDEMIOLOGY

Recovery from COVID-19 infection is defined as an absence of fever for three consecutive days with improvement in other symptoms and two negative results for SARS-CoV-2 done 24 hours apart.⁹ As per the initial reports from China, the mean recovery time appeared to be around 2 weeks for mild cases and 3–6 weeks for patients with severe disease.¹⁰ However, the recovery course can be variable depending on the age, presence of comorbidities with hospitalised severe COVID-19 cases often having prolonged symptoms and varying disability. The road to recovery following COVID-19 infection is often a long and arduous one with persistent symptoms seen in a significant proportion of individuals. Recent reports have highlighted the development of new symptoms or persistence/worsening of pre-existing symptoms in patients with mild disease and who have recovered from the initial episode of COVID-19 infection. A review of the 16 published studies (table 1) reported 'post-COVID-19 syndrome' in 30%–87.4% of patients recovered from COVID-19.^{9 11–25} Initial reports from Italy involving 143 patients who were evaluated following COVID-19 infection revealed that 87.4% had at least one symptom or the other (one or two symptoms: 32%; three or more symptoms: 55%) even after 60 days of recovering from the initial infection.⁹ Similarly, in a survey among 350 patients with COVID-19 in the USA, only 39% of those who were hospitalised returned to baseline health between 14 and 21 days following diagnosis.¹¹ In the 'UK COVID-19 Symptom Study',²⁶ nearly 10% of COVID-19 positive patients reported unwell even after 3 weeks. In a recently published study from the UK, among the 100 COVID-19 survivors, fatigue was the most common persistent symptom (60.3%) followed by breathlessness (42.6%) and neuropsychological symptoms (23.5%).¹⁸ In one of the largest studies from China comprising 1733 patients, Huang *et al*¹⁵ reported post-COVID-19

Table 1 Review of the clinical studies on post-COVID-19 syndrome

Author/site/no. of participants	Severity of initial infection	Follow-up duration/mode of follow-up	Prevalence post-COVID-19 syndrome	General sequelae	Respiratory sequelae	CV sequelae	Neurological sequelae	GI sequelae	Impaired QoL
Carfi et al/Italy/n=143 ⁹	O ₂ requirement: 53.8% NIV: 14.7% IMV: 4.9% ICU care: 12.6%	60.3±13.6 days* in-person	87.4%	Fatigue: 53.1% Joint pain: 27.3%	Dyspnoea: 43.4% Cough: 15%	Chest pain: 21.7%	Anosmia/ageusia: 15% Headache: 10%	NR	Yes (44.1%)
Tenforde et al/USA/n=274 ¹¹	NR	2–3 weeks/ telephone survey	34%	Fatigue: 35%	Cough: 43% Dyspnoea: 29%	NR	NR	NR	NR
Liang et al/China/n=76 ¹²	Mild: 91% Severe: 9%	90 days/ In-person	NR	Fatigue: 60% Fever: 20%	Dyspnoea: 61% Cough: 60% Sputum: 43%	Chest tightness: 62% Palpitations: 62%	NR	Diarrhoea: 26%	NR
Arnold et al/UK/n=110 ¹³	Mild: 24.5% Moderate: 59.1% Severe: 16.3%	8–12 weeks/in-person	74%	Fatigue: 39% Myalgia: 22.7% Fever: 0.01%	Dyspnoea: 39% Cough: 11.8%	Chest pain: 12.7%	Insomnia: 24% Anosmia: 11.8% Headache: 1.8%	Diarrhoea: 0.01%	Yes
Garrigues et al/France/n=120 ⁴	ICU: 20%	3–4 months/ telephone survey	NR	Fatigue: 55%	Dyspnoea: 41.7% Cough: 16.7%	Chest pain: 10.8%	Sleep disturbance: 30.8% Memory loss: 34.2% Attention disorder: 26.7% Anosmia/ageusia: 10.8%–13.3%	NR	Yes (21.5%)
Huang et al/China/n=1733 ¹⁵	Admitted without O ₂ requirement: 25% O ₂ requirement: 68% HFNC/NIV: 6% ECMO/IMV: 1%	6 months/in-person	76%	Fatigue: 63% Joint pain: 9% Muscular pain: 2% Fever: 0.1%	Dyspnoea: 23% Sore throat: 4%	Palpitations: 9% Chest pain: 5%	Sleep disturbance: 26% Anosmia: 11% Agusia: 7% Headache: 2%	Diarrhoea/vomiting: 5%	Yes
Xiong et al/China/n=538 ¹⁶	Mild: 61.5% Severe: 33.5% Critical: 5%	97 days/in-person	49.6%	Fatigue: 28.3% Sweating: 23.6% Arthralgia: 7.6% Chills: 4.6% Myalgia: 4.5%	Polypnoea: 21.4% Cough: 7.1% Throat pain: 3.2% Sputum: 3%	Chest pain: 12.3% Increased resting HR: 11.2% New onset HTN: 1.3%	Somniphathy: 17.7% Anxiety: 6.5% Depression: 4.3% Dysphoria: 1.7%	NR	NR
Canvalho-Schneider et al/France/n=150 ¹⁷	Mild/moderate: 77.3% Severe: 22.7%	60 days/telephone survey	66%	Fatigue: 40% Joint pain: 16.3%	Dyspnoea: 30%	Chest pain: 13.1% Palpitations: 10.9%	Anosmia/ageusia: 22.7%	Diarrhoea: 11.5%	NR
Halpin et al/UK/n=100 ⁸	O ₂ requirement: 78% NIV: 30% IMV: 1% ICU care: 32%	48 days/ telephone survey	NR	Fatigue: 64%	Dyspnoea: 40%	NR	PTSD: 31% Difficulty in concentration: 22%	Dysphagia: 8%	NR
Logue et al/USA/n=177 ¹⁹	Asymptomatic: 6.2% Mild: 84.7% Moderate to severe: 9%	169 days/in-person	30%	Fatigue: 13.6%	NR	NR	'Brain fog': 2.3%	NR	29.9%
Chopra et al/USA/n=488 ²⁰	NR	60 days/telephone survey	32.6%	NR	Dyspnoea: 22.9% Cough: 15.4%	NR	Anosmia/ageusia: 13.1%	NR	NR
Moreno-Pérez et al/Spain/n=277 ¹	Mild: 34.3% Moderate-Severe: 65.7%	77 days/in-person	50.9%	Fatigue: 34.8% Myalgia: 19.6%	Dyspnoea: 11% Cough: 2.1%	NR	Anosmia/ageusia: 21.4% Headache: 5.4%	Diarrhoea: 10.5%	66.9%
Pereira et al/UK/n=38 ²²	Mild: 100%	7–8 months/in-person	55%	Fatigue: 57%	Dyspnoea: 24%	NR	Anosmia: 29% Difficulty in concentration: 24%	NR	NR

Continued

Table 1 Continued

Author/site/no. of participants	Severity of initial infection	Follow-up duration/mode of follow-up	Prevalence post-COVID-19 syndrome	General sequelae	Respiratory sequelae	CV sequelae	Neurological sequelae	GI sequelae	Impaired QoL
Taboada <i>et al</i> /Spain/n=91 ²³	ICU: 100%	6 months/in-person	84%	Asthenia: 37% Myalgia: 37% Arthralgia: 29%	Dyspnoea: 57% Cough: 14.4%	Chest pain: 8.8%	Anosmia: 11% Insomnia: 30.8%	NR	Yes (67%)
Mahmud <i>et al</i> /Bangladesh/n=355 ²⁴	Mild: 62% Moderate: 26% Severe: 11%	30 days/telephone survey	46%	Fatigue: 33% Rash: 0.6% Myalgia: 0.6%	Cough: 8.5% Dyspnoea: 7%	Palpitation: 1.4% Bradycardia: 0.6% Chest pain: 0.8% New onset HTN: 0.6%	Headache: 3.4% Vertigo: 2.3% Insomnia: 2.3% Anosmia: 2% Memory disturbance: 0.6%	New onset dyspepsia: 1.4%	NR
Sonnweber <i>et al</i> /Austria/n=145 ²⁵	O ₂ requirement: 66% NIV: 3% IMV: 2.7%	60–100 days/in-person	NR	Night sweats: 24%	Dyspnoea: 36% Cough: 17%	NR	Sleep disorders: 22% Hyposmia/anosmia: 19%	Diarrhoea: 9%	NR

*Mean±SD.

†Median.

CV, cardiovascular; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; HFNC, high-flow nasal cannula; HR, Heart Rate; HTN, hypertension; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; NR, not reported; O₂, oxygen; PTSD, post-traumatic stress disorder; QoL, Quality of Life.

syndrome in 76% of the subjects. Increasing numbers of patients are being evaluated for symptoms such as chronic cough, breathlessness, fatigue, weakness and myalgias post-COVID-19 infection. In addition, cardiovascular and cerebrovascular conditions such as stroke or acute myocardial infarction (MI) are frequently being reported in the convalescent phase of COVID-19 infection. All these pieces of evidence point towards a clinical syndrome consisting of a constellation of signs and symptoms following recovery from COVID-19. This review tends to highlight the ever-expanding spectrum of post-COVID-19 syndrome with its varied manifestations.

PATHOPHYSIOLOGY

SARS-CoV-2 predominantly affects the respiratory system leading to pneumonia and acute respiratory distress syndrome (ARDS). In addition, the acute phase of infection is also characterised by multisystem involvement such as the central nervous system manifesting as stroke, encephalitis or the cardiovascular system leading to an acute coronary syndrome (ACS), myocarditis and arrhythmias.¹ These manifestations of SARS-CoV-2 infection are often attributed to the occurrence of a cytokine storm with elevated levels of circulating cytokines such as interleukin (IL) 1, IL-2 and IL-6, all of which have a deleterious effect on various organ systems.¹ In addition, presence of a hypercoagulable state can explain the increased thrombotic events in COVID-19 infection. Though the exact pathophysiological mechanism of this novel clinical entity remains unclear, it can mostly be attributed to the inflammatory cytokine response and a hypercoagulable state that persists even following clinical recovery from COVID-19 infection.¹ A delayed clearance of virus leading to low levels of viraemia often culminates in a chronic low-grade inflammatory response. This could explain most of the symptoms of chronic fatigue, myalgias, joint pains and weakness occurring in the convalescent phase of COVID-19. Similar findings have been observed in other viral infections such as the postchikungunya chronic inflammatory rheumatism wherein chronic synovitis from virus-affected joints or the persistence of viral particles leading to an ongoing inflammatory response being the prominent cause.²⁷ Survivors of Ebola virus disease too have reported features of chronic fatigue, which had been attributed to the underlying inflammatory response.²⁸ In addition, a persistent hypercoagulable state could potentially explain an increased occurrence of stroke and ACS following recovery from COVID-19. Other theories for a post-COVID-19 sequela include a potential autoimmune-mediated mechanism wherein SARS-CoV-2 could act as an immune trigger leading to molecular mimicry and host cell damage.²⁹

SPECTRUM OF PRESENTATION IN POST-COVID-19 SYNDROME

Clinical features in patients with post-COVID-19 syndrome can vary from milder symptoms such as myalgias, easy fatigability, anxiety, low-grade fever, headaches to severe symptoms such as breathlessness, palpitations and chest pain.^{9 11 18} Symptoms such as chest pain and breathlessness are alarming following recovery from COVID-19. It is imperative to rule out ACS and myopericarditis in patients presenting with acute onset chest pain. Similarly, pulmonary thromboembolism and residual pulmonary fibrosis too must be evaluated in patients with persistent/new-onset breathlessness.^{1 18}

Systemic manifestations in this syndrome range from pulmonary, neurological, cardiovascular and musculoskeletal (figure 1).

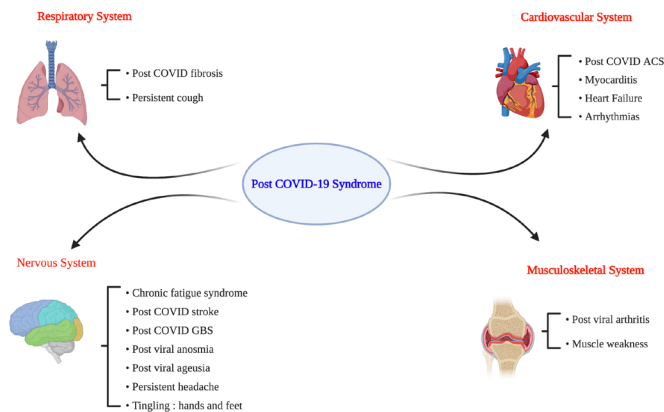


Figure 1 Diagrammatic representation of the clinical spectrum of post-COVID-19 syndrome (created with Biorender.com). ACS, acute coronary syndrome; GBS, Guillain-Barré syndrome.

Pulmonary sequelae

It is well understood that the lung is the predominant organ affected in SARS-CoV-2 and hence pulmonary sequelae to the active infection is increasingly being detected. The major respiratory symptoms in patients with post-COVID-19 sequelae include persistent cough (mostly dry) along with shortness of breath. Dyspnoea is the most common persistent symptom following recovery from COVID-19 and has been reported in 7%–61% of patients.^{9–11–25} In patients with active COVID-19 infection, the major radiological findings include consolidation and ground-glass opacities (GGOs) predominantly in the lung peripheries and lower lobes along with other patterns such as interlobular and intralobular septal thickening, pleural effusion, pericardial effusion, bronchiectasis, bronchial wall thickening, reverse halo, subpleural lines and fibrotic bands.³⁰ Among these, the most common sequelae that have garnered attention is post-COVID-19 pulmonary fibrosis (figure 2), while most others tend to regress after the acute infection subsides. In a

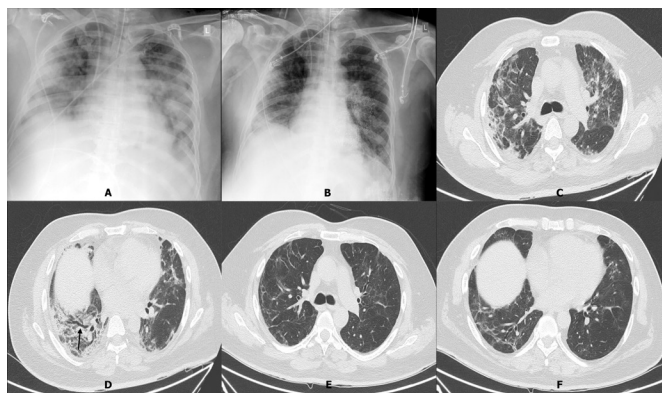


Figure 2 Figure showing post-COVID-19 pulmonary fibrosis and response to oral antifibrotics and corticosteroids in a 42-year-old man who presented with bilateral COVID-19 pneumonia (figure 2A and 2B). HRCT of the chest (figure 2C and 2D) done 1 month following hospital discharge owing to persistent exertional dyspnoea showing fibrotic opacities with reticulations, traction bronchiectasis (figure 2D: black arrow) and areas of interlobular septal thickening in bilateral lung fields suggestive of post-COVID-19 pulmonary fibrosis. HRCT done 2 months later (figure 2E and 2F) following treatment with oral corticosteroids and pirfenidone showing marked resolution in the extent of pulmonary fibrosis. HRCT, high-resolution CT.

study, it was reported that predischarge CT scans with GGOs were found in 79.2% of patients, which improved in follow-up scans, while fibrosis was seen in 44.8% scans and fibrous stripes in 36.8%. Fibrosis also showed improvement in follow-up scans in 65.3%, while fibrous stripes once developed did not improve in any of the scans.³¹ In a systematic review published by Polak *et al*,³² which studied pulmonary pathology findings of reported cases, fibrosis was seen in 22% of patients. In a study by Xu *et al*,³³ fibrinous exudates were seen in the alveolar lumen, which is reflected in radiological scans as fibrosis. Development of fibrosis can be rapidly progressive also, with advent as early as 10 days in a case report.³⁴ In postmortem analysis too, there has been evidence of fibrosis with honeycombing like interstitial lung diseases along with diffuse alveolar damage.³⁵ Although these findings can be confounding due to ventilator-induced lung injury (VILI) however, with the use of lung-protective ventilation in most centres, fibrosis cannot be attributed only to VILI.

Post-COVID-19 fibrosis may present with shortness of breath and cough or can be asymptomatic owing to minimal scarring of the lung parenchyma. Since CDC advises clinical criteria for discharging patients and does not pay heed to radiology, these patients might be overlooked and the symptoms might be attributed to deconditioning.³⁶ It is imperative to look for post-COVID-19 fibrosis especially in patients with residual dyspnoea after ruling out other differential diagnoses that can be seen post-COVID-19 infection including neuromuscular weakness, deconditioning and cardiovascular causes. There are various mechanisms implicated in the development of fibrosis secondary to COVID-19 infection. In the previous SARS pandemic, lung fibrosis as a sequelae to initial infection has been documented.⁶ The proposed mechanism included the role of transforming growth factor-beta (TGF- β) and connective tissue growth factor, which were elevated in alveolar epithelial cells leading to fibronectin deposition in the extracellular matrix and hence fibrosis.³⁷ There occurs a direct stimulation of TGF- β by the nucleocapsid protein of the SARS-CoV-1 and since the nucleocapsid core of the SARS-CoV-2 is nearly 90% similar to SARS-CoV-1, this mechanism may hold true. Another postulated mechanism includes downregulation of ACE, which further downregulates angiotensin II leading to TGF- β stimulation. In addition, there seems to be an additional role of oxidative stress and free radical mediated lung injury, a finding similar to that seen in idiopathic pulmonary fibrosis (IPF).³⁸ There seems to be a homology in the cytokine profiles of IPF and COVID-19 patients suggesting similar pathogenesis of lung fibrosis.³⁸ However, it is still unclear as to why some individuals have complete recovery of lung functions following an initial assault by the virus and why some have unregulated cellular proliferation with an abundant accumulation of fibroblasts leading to excessive deposition of collagen and extracellular matrix proteins.³⁹ There have been some predisposing factors associated with the development of post-COVID-19 fibrosis as reported Yu *et al*.⁴⁰ The authors found that patients with lung fibrosis following initial infection were older with a median age of 54 years and had higher levels of inflammatory markers such as C reactive protein, lactate dehydrogenase and IL-6. In addition, these patients also had lower absolute lymphocyte counts, longer hospital stay, initial presentation with shortness of breath and higher respiratory rate, requirement of intensive care unit admission or requirement of longer antiviral therapy and pulsed steroid therapy. This study also found interstitial thickening, irregular interface, coarse reticulation and parenchymal band as early radiological predictors of development of fibrosis.⁴⁰

Cardiovascular sequelae

Cardiovascular complications in COVID-19 range from ACS to myocarditis, pericarditis and cardiac arrhythmias. Most of the complications often occur within the first or second week of presentation. ACS and myocarditis are two important cardiovascular complications that often have a poor prognosis and are associated with a high mortality rate. Cardiac involvement in COVID-19 has been ascribed to multiple mechanisms such as proinflammatory milieu due to cytokine storm, direct viral invasion of the myocytes, hypercoagulable state with thromboembolic phenomenon, coronary plaque instability or a demand-supply mismatch leading to ACS.^{1,41}

Cardiac manifestations are not only limited to the period of active COVID-19 infection and can occur even during the convalescent phase. Patients are at a heightened risk for ACS during the convalescent phase, and post-COVID-19 MI can occur as a result of the coronary plaque instability due to ongoing inflammation. In addition, a persistent hypercoagulable state and endothelial dysfunction postinfection with the novel SARS-CoV-2 too can be the postulated causes for an ACS precipitating even after recovering from COVID-19 infection.¹ Myocardial inflammation is not only related to acute COVID-19 or symptomatic COVID-19 cases as was previously thought. In a recent series from Germany, Puntmann and colleagues⁴² using cardiac MRI (CMR) reported an ongoing myocardial inflammation in 60/100 patients despite having recovered from COVID-19 infection. Three patients with significant cardiac involvement had active lymphocytic inflammation on endomyocardial biopsy. All these patients had undergone a CMR following resolution of their respiratory symptoms and a negative reverse transcription PCR test after a minimum interval of 2 weeks from the original diagnosis. Most of these patients were either asymptomatic or had mild to moderate symptoms, while those with active cardiac symptoms were excluded. All this evidence points to ongoing cardiac inflammation (perimyocarditis) even in the convalescent phase of the disease.

This ongoing myocardial inflammation, oedema and ventricular dysfunction could be one of the reasons for symptoms such as chest pain and breathlessness in post-COVID-19 convalescent phase (figure 3). In addition, ongoing inflammation can further lead to myocardial scarring and form a nidus for life-threatening ventricular arrhythmias especially in elderly patients and those with comorbidities.⁴³ All of this has far-reaching consequences keeping in mind the huge burden of recovered cases and ongoing myocardial inflammation and subclinical myocardial dysfunction that might present later on in life. This calls for better risk stratification in patients who are elderly or having multiple comorbidities using biomarkers such as cardiac troponins and judicious use of CMR in patients with elevated biomarkers to detect ongoing myocardial inflammation. In addition, use of cardioprotective therapies such as statins⁴⁴ or even sodium-glucose cotransporter-2 inhibitors⁴⁵ can potentially decrease the long-term sequelae in these patients. Previous studies have shown that higher New York Heart Association functional class, signs of inflammation on immunohistology, detection of viral genome or CMR features of active inflammation are associated with poor outcomes.⁴⁶ Post-COVID-19 cardiac syndrome comprises patients with a hypercoagulable state and ongoing inflammation manifesting either as an ACS or as a sequelae of myocarditis with left ventricular dysfunction or persistent myocardial inflammation culminating in arrhythmias or heart failure. Data from the previous SARS pandemic too had suggested a long-term sequelae following infection with SARS coronavirus.⁴⁷

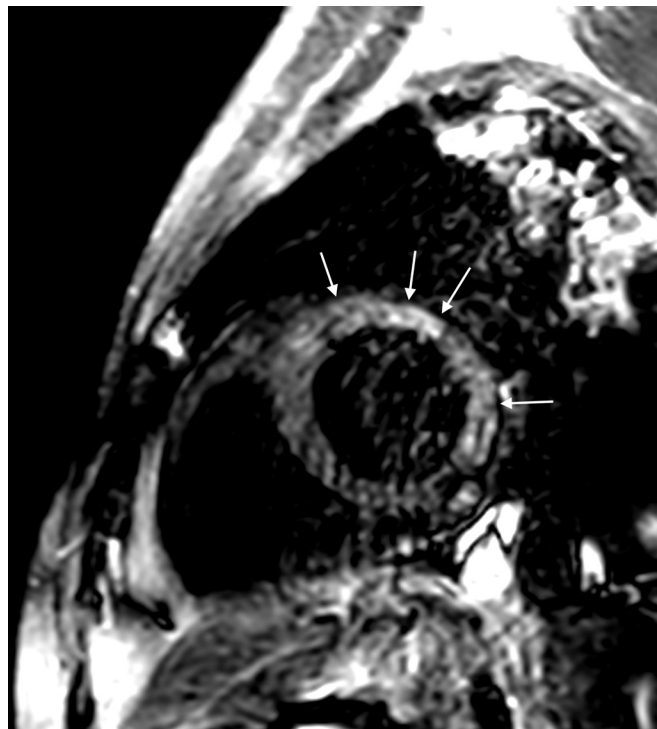


Figure 3 Cardiac MRI (axial T2-STIR image at midventricular level) in a 30-year-old man done a month following recovery from COVID-19 infection showing oedema in the anterior and lateral wall of the left ventricle (white arrows) suggestive of persistent myocardial inflammation and subclinical myocarditis.

Other important cardiovascular sequelae includes the occurrence of thromboembolic events especially venous thromboembolism (VTE) following recovery from COVID-19 infection. A single-centre study from the USA comprising 163 patients documented VTE in 2.5% of recovered patients at 30 days following discharge with a majority of them being segmental pulmonary embolism, intracardiac thrombus and ischaemic stroke.⁴⁸ Similar data from retrospective studies from UK too reported VTE rates of 4.8% and 7.2% in patients following COVID-19 infection.^{49,50} Occurrence of pulmonary thromboembolism following recovery from COVID-19 infection can be life-threatening especially if associated with haemodynamic instability. Since COVID-19 infection is associated with a hypercoagulable state, there occurs a heightened risk for VTE during the convalescent phase of the disease. This was highlighted in a recently published report of acute pulmonary thromboembolism in a 52-year-old woman following recovery from COVID-19.⁵¹

Neurological sequelae

Neurological manifestations in COVID-19 often comprise of meningitis, encephalitis, acute disseminated encephalomyelitis, immune-mediated acute haemorrhagic necrotising encephalopathy, corticosteroid-responsive encephalopathy, stroke (ischaemic/haemorrhagic), myelitis and Guillain-Barré syndrome (GBS).⁵² Neurological manifestations are often due to direct viral invasion, immunological reaction, hypoxic metabolic changes in the brain or following a hypercoagulable state due to systemic inflammation in COVID-19. Most of these acute presentations are concurrent with the disease process; however, some manifestations such as stroke or GBS may be postinfectious during the convalescent phase of COVID-19 infection.

Post-COVID-19 GBS

GBS is an acute/subacute inflammatory polyradiculoneuropathy that is often characterised by progressive limbs or cranial-nerve weakness accompanied by loss of deep tendon reflexes and sensory and dysautonomic symptoms.⁵³ Most of the cases occur 2–4 weeks following an acute respiratory or gastrointestinal infection. This autoimmune disorder occurs due to the production of antibodies that cross-react with gangliosides and glycolipids present in myelin in the peripheral nervous system (molecular mimicry). This leads to the demyelination of the peripheral nervous system along with axonal damage.⁵⁴ GBS has been previously associated with other coronavirus infections such as the SARS-CoV and MERS-CoV infection and has been even documented in patients with COVID-19.^{55–56} GBS following COVID-19 infection has been described as either postinfectious or parainfectious. Postinfectious refers to patients with GBS arisen in the convalescent phase after the SARS-CoV-2 infection has resolved, while parainfectious is defined as GBS that evolves during active COVID-19 infection. Zhao *et al*⁵⁷ described the first case of GBS associated with SARS-CoV-2 infection that had a parainfectious course, while Padroni *et al*⁵⁸ reported GBS in 70-year-old woman 4 weeks following COVID-19 infection. In a review of 23 reported cases of GBS associated with COVID-19 infection by Agosti *et al*,⁵⁹ postinfectious cases were more common as compared with the parainfectious ones.

Post-COVID-19 stroke

COVID-19 infection may provoke the occurrence of cerebrovascular diseases, mainly acute ischaemic stroke as well as venous and haemorrhagic strokes. Most of these events occur in young individuals without antecedent risk factors and often with mild or no symptoms of COVID-19.⁶⁰ A majority of these stroke events occur concurrently with the disease process; however, there are reports of delayed occurrence of stroke following COVID-19 infection (figure 4). Patients recovering from COVID-19 infection often have a higher risk of stroke owing to the presence of a hypercoagulable state along with endothelial dysfunction.⁶¹ Systemic inflammation in COVID-19 leads to a hypercoagulable state along with endothelial dysfunction that often persists despite having recovered from acute infection. SARS-CoV-2 has also been shown to induce central nervous system vasculitis leading to microcirculatory vasoconstriction and endothelial damage with subsequent ischemia and apoptosis. In addition, COVID-19 induced myocarditis and cardiomyopathy may

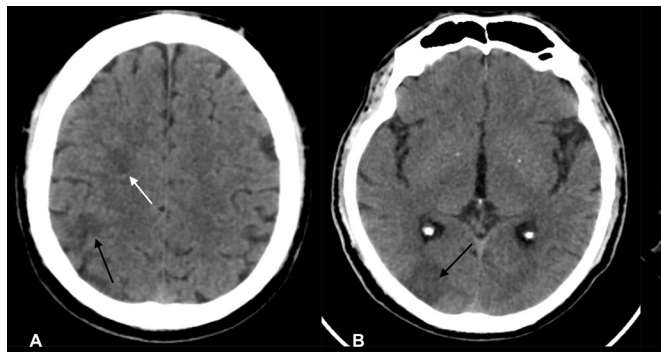


Figure 4 CT brain (figure 4A and B) of a post-COVID-19 45-year-old man with no prior comorbidities and presenting with acute haemiplegia. CT showed infarcts in right parieto-occipital region (figure 4A and B: black arrows) as well as in centrum semiovale (figure 4A: white arrow).

lead to cardioembolic stroke even in the convalescent phase of COVID-19 infection.¹

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS)

ME/CFS is a chronic multisystem illness that has variable constitutional and neurocognitive manifestations. This is increasingly being documented in patients recovering from COVID-19 infection whereby they report as a lack of well-being. The symptoms mostly comprise of a feeling of extreme exhaustion, non-restorative sleep, muscle aches, headaches and having a trouble in thinking/remembering often described as ‘fog’. Post-infectious fatigue is not specific to COVID-19 infection but has been observed in previous pandemics such as the SARS in 2003 and the H1N1 pandemic in 2009.⁶² This has been often ascribed to the ‘cytokine storm’ leading to release of a flurry of cytokines such as IL-1, IL-2 and IL-6. These proinflammatory cytokines affect the neurological control of the ‘Glymphatic System’.⁶³ In the study by Tansey *et al*⁶⁴ during the previous SARS pandemic, fatigue was reported in 64% of patients at 3 months and 60% at 12 months, which was often associated with sleep disturbances. Similarly, Lam *et al*⁵ documented chronic fatigue in 40.3% and ME/CFS in 27.1% over a 4-year follow-up of patients recovered from SARS infection. Keeping in mind the huge burden of patients recovering from COVID-19 infection, it is expected that a significant proportion of them would present with ME/CFS adding to the already overburdened and depleted healthcare system. As the COVID-19 pandemic continues to evolve, there has been some evidence regarding the occurrence of ME/CFS and its impact on the healthcare system. In a report published by the CDC, wherein a telephonic survey was conducted among COVID-19 outpatients with mild symptoms, it was seen that nearly 35% of them documented a lack of return to their ‘usual state of health’ even 2–3 weeks post testing positive for SARS-CoV-2. A majority of them were elderly above 50 years of age with fatigue being reported in 35% of them.¹¹ This is in sharp contrast to the outpatient influenza patients wherein nearly 90% of them recovered in the first 2 weeks of illness.⁶⁵

Other neurological sequelae

These include persistent loss of smell (anosmia) or taste (ageusia) even after recovering from COVID-19 infection. Viral infections are a leading cause for anosmia in adults accounting for nearly 40% of the cases.⁶⁶ Similar findings too have been reported in patients with COVID-19 infection. In a survey among 187 patients with COVID-19, 113 reported impairment of smell or taste at baseline. At 4 weeks of follow-up, an altered sense of smell or taste was reported in 69 patients (36.9%), of whom 12 reported that the symptom was unchanged or had worsened. In addition, this study also reported a significant proportion of patients having persistent cough (39.7%), dyspnoea (39%), headache (23.7%) and malaise (13.9%) even after recovering from COVID-19.⁶⁷ In addition, in our experience, an increasing proportion of patients present with persistent headache or with tingling and numbness of hands and feet.

Musculoskeletal sequelae

Muscle weakness and fatigue are commonly reported features in SARS-CoV-2.⁶⁸ It may be mild as part of the constitutional symptoms or severe as in rhabdomyolysis.⁶⁹ It was seen in the previous coronavirus outbreak that myopathic changes are not uncommon in the illness.⁷⁰ Thus, it is pertinent to note for muscular changes, fatigue and weakness developing post illness. It has been well documented that critical illness myopathy can

develop in patients hospitalised for long time or following a critical illness and can be seen in post-COVID-19 patients too.⁷¹ Various risk factors described previously in a meta-analysis include female gender, sepsis, hyperglycaemic states, use of neuromuscular blockers during hospital stay and a lengthy mechanical ventilation.⁷² A recent study revealed that a greater muscle mass loss was observed in COVID-19 obese patients.⁷³ It is seen that severe catabolism occurs during acute phase of the illness, which leads to muscular loss in the latter phase owing to decreased anabolism. It is postulated that leptin is increased during the acute phase along with other inflammatory cytokines that affects the hunger. Additionally, activation of the ubiquitin-proteasome system by tumour necrosis factor- α and transforming growth factor beta in inflammatory states leads to accelerated muscle protein breakdown and loss of muscle mass. Muscle protein synthesis is decreased by the action of insulin like growth factor and mammalian target of rapamycin pathway. Another potential pathway for muscular destruction is mitochondrial dysfunction secondary to metabolic stressors, causing a depletion of the mitochondrial ATP and enhancing free radical release leading to further proteolysis.⁷⁴

Endocrine and gastrointestinal sequelae

New onset diabetes and diabetic keto-acidosis has been reported in non-diabetics even weeks after an initial bout of COVID-19.⁷⁵ This could be due to viral injury to the pancreatic cells or as a consequence of immunological and inflammatory damage. In addition, patients with COVID-19 administered steroids for a considerable proportion may develop diabetes especially the pre-diabetics. Data on the incidence and long-term outcomes of new onset diabetes is still unclear with the ongoing CoviDiab registry expected to provide some robust evidence in this direction.⁷⁶ Other endocrine manifestations include reports of subacute thyroiditis and thyrotoxicosis occurring days after resolution of active COVID-19 infection.^{77,78} The gastrointestinal manifestations in the recovery phase of COVID-19 infection include diarrhoea, dyspepsia and irritable bowel syndrome. This occurs as a result of the alteration of the gut microbiome with abundance of opportunistic infectious agents.⁷⁹

MANAGEMENT

Post-COVID-19 syndrome calls for an interdisciplinary management strategy often comprising general physicians/pulmonologists, intensivists, cardiologists, neurophysicians and rehabilitation specialist. Most of the worst affected countries have already started specialised clinics for the care of these patients. A majority of symptoms are self-limiting and often improves over a period of time. Self-monitoring of oxygen saturation using pulse oximeters would often allay the fears of silent hypoxia especially in individuals with lung fibrosis or symptoms of breathlessness. A fall in $\text{SpO}_2 > 4\%$ is abnormal and warrants prompt medical care. It is important to monitor patients for development of fibrosis through evaluation of functional status (6 min walk test), serial pulmonary function testing and chest radiology. There also lies the role of pulmonary rehabilitation in recovery phase that helps in alleviation of anxiety and exercise endurance and promotes self-care.⁸⁰

There have been many potential therapies that have been postulated for prevention of post-COVID-19 fibrosis.³⁸ These can be subdivided into antivirals, immunosuppressive agents and antifibrotics. It is postulated that early onset of antiviral treatment might lead to better outcomes with respect to viral illness as well as its sequelae. Immunosuppressive agents like steroids

and biologicals such as IL-6 inhibitors might be beneficial in suppressing inflammatory response and subsequently lower the levels of fibrogenic mediators. Antifibrotic agents like pirfenidone and nintedanib have also been seen as potential therapies (figure 2). These drugs besides their antifibrotic properties also have potent antioxidant, anti-inflammatory activities and can lead to downregulation of ACE receptor expression, making their trial in these patients a legit choice.⁸¹ There are novel therapies that have been suggested like use of metformin, which acts mainly by increasing the pH of the vesicles and thereby inhibiting viral infection.⁸² Spironolactone has also been previously studied in chemotherapy and radiotherapy induced lung injury as well as heart failure. It supposedly acts by its antioxidant properties, as well as by affecting the aldosterone pathway which, in turn, may decrease the fibrosis.³⁸ It has been seen previously that fibrinolysis using urokinase and streptokinase decreased mortality in terminal ARDS patients,⁸³ while another study using tissue plasminogen activator in rats had shown better partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2) levels, thus making it a potential therapy.⁸⁴ It tends to decrease lung leak by probably decreasing neutrophil oxidative stress, preventing injury and may, in turn, decrease fibrosis. Other drugs that deserve a mention and have ongoing trials include hyperbaric oxygen, tetrandrine and colony stimulating factors (table 2). Our experience with such patients shows a protracted course with improvement occurring over several months and most of them requiring domiciliary oxygen therapy.

It may be imperative to screen COVID-19 patients with high-risk factors such as multiple comorbidities for the presence of cardiac injury using biomarkers such as troponins and N-terminal pro B-type natriuretic peptide. Both of them have been shown to be effective in short-term risk stratification in these patients. Patients with COVID-19 and acute cardiac injury or myocarditis should be serially followed up every 3–6 months with an echocardiogram or preferably CMR or echocardiographic strain imaging. Patients with COVID-19 and ST-segment elevation MI who have been treated as per standard protocol should be continued on post-MI therapies including ACE inhibitors or beta-blockers along with serial imaging follow-up for ventricular functions. There is no consensus regarding the extended duration of prophylactic anticoagulation among patients at risk of VTE in post-COVID-19 recovery. The American College of Chest Physicians (CHEST) guidelines on prevention, diagnosis and treatment of VTE in COVID-19 recommends ‘only inpatient anticoagulant thromboprophylaxis’ over ‘inpatient plus extended thromboprophylaxis after hospital discharge’. In addition, the guideline statement does mention the role of extended thromboprophylaxis in patients with COVID-19 at low risk of bleeding ‘if emerging data on the post-discharge risk of VTE and bleeding indicate a net benefit of such prophylaxis’.⁸⁵

Management of stroke and GBS is similar to that in COVID-19 negative patients. There is no definite therapy for chronic fatigue syndrome; however, treatment would focus on the role of cognitive-behavioural therapy, graded exercise therapy and occasionally use of pharmacotherapy with antidepressants. In addition, professional counselling, balanced diet and nutritional supplements would help recover from the illness.⁸⁶ Treatment may be considered for anosmia persisting beyond 2 weeks. These would include olfactory training that involves repeated sniffing of a given set of odorants for at least 20 s twice a day over 3 months or even longer. In addition, oral and intranasal corticosteroids too have been used in postviral anosmia along with intranasal sodium citrate, intranasal vitamin A and omega-3 capsules with varying effects.⁸⁷ There is no specific treatment

Table 2 Review of preclinical/clinical trials on antifibrotic therapies in COVID-19

S no	Trial number/site	Drug/therapy	Drug dose/duration	Mechanism of action	Trial design/participant	Comparator arm	Primary end point	Phase	Current status
1.	NCT04338802/China	Oral nintedanib	150 mg BD × 8 weeks	Antifibrotic	RCT, open label, single centre, 96 subjects	Placebo	Change in FVC after 8 weeks of treatment compared with baseline	II	Ongoing
2.	NCT04282902/China	Oral pirfenidone	Two tablets (200 mg each) three times a day 4 weeks or longer	Antifibrotic	RCT, open label multicentre; 294 participants (147 each arm)	Standard treatment	<ul style="list-style-type: none"> ▶ Improvement in HRCT image at 4 weeks. ▶ Absolute change in pulse oxygen from baseline. ▶ Absolute change in blood gas from baseline. ▶ Absolute change in total score of King's brief questionnaire for interstitial pulmonary disease from baseline at week 4. 	III	Ongoing
3.	NCT04288102/China	Human umbilical cord-derived mesenchymal stem cells	Intravenous three doses of UC-MSCs (4.0 × 10 ⁷ cells/time) at day 0, day 3, day 6 plus standard of care	Reduces non-productive inflammation and affects tissue regeneration	RCT, multicentre; 100 subjects	Intravenous three doses of placebo (saline containing 1% human serum albumin) at day 0, day 3, day 6 plus standard of care	<ul style="list-style-type: none"> ▶ Change in lesion proportion of full lung volume from baseline to day 28. Secondary endpoint: <ul style="list-style-type: none"> ▶ Pulmonary fibrosis related morphological features in CT scan at day 90. ▶ Change in FVC and DLCO. 	II	Ongoing
4.	NCT04279197/China	Fuzheng Huayu (traditional Chinese medicine)	1.6 g (0.4 g each tablet) three times a day, plus basic treatment (respiratory function rehabilitation training +vitamin C tablets 0.2 g three times a day)	Unclear	RCT, double blind multicentre, 160 participants	Basic treatment (respiratory function rehabilitation training +vitamin C tablets 0.2 g three times a day) plus placebo	<ul style="list-style-type: none"> ▶ Evaluation of Pulmonary fibrosis Improvement on HRCT ▶ Improvement in 6 min walk test distance after 24 weeks 	II	Ongoing
5.	NCT04432298 Italy	Pamrevlumab	35 mg/kg on days 1, 7, 14 and 28 for a total of four infusions over 4 weeks	Monoclonal antibody against connective-tissue growth factor: antifibrotic	Randomised, double-blind, placebo-controlled; 130 subjects	Placebo: 35 mg/kg on days 1, 7, 14 and 28 for a total of four infusions over 4 weeks	Proportion of subjects who never received mechanical ventilation and/or ECMO and alive	II	Ongoing
6.	NCT04334460, Brazil and USA	B-2660–204	Oral B-2660–204 (dose: NA)	<ul style="list-style-type: none"> ▶ Small molecule inhibitor of calpain 1, 2 and 9. ▶ Antifibrotic effect: significant reductions in the alpha smooth muscle actin and collagen 1 in lung tissue. 	RCT, double blind multicentre, placebo-controlled; 120 subjects	Placebo	<ul style="list-style-type: none"> ▶ Time to recovery. ▶ Change in oxygenation. ▶ Reduction in viral burden, improvement in cardiopulmonary function and functional recovery. 	II	Ongoing
7.	NCT0430831/China	Tetrandrine (traditional Chinese medicine)	Tetrandrine 60 mg once a day × 6 days	<ul style="list-style-type: none"> ▶ Antagonist of calmodulin: anti-inflammatory effects. ▶ Inhibit fibroblasts – inhibiting pulmonary fibrosis. 	▶ RCT, open label single centre; 60 subjects	Control cohort: standard treatment protocol	Survival rate in 12 weeks follow-up	IV	Ongoing
8.	NCT04334265/China	Anluohuaxian (traditional Chinese medicine)	Anluohuaxian +regular treatment group 6 g each time, twice a day	Antifibrotic	Randomised, open label multicentre; 750 participants	Regular treatment group	<ul style="list-style-type: none"> ▶ Changes in HRCT of the lung in 3 months. ▶ Change in 6 min walking distance in 3 months. 	NR	Ongoing
9.	NCT04319731/USA	Human amniotic fluid	Intravenous 10 mL purified (acellular) amniotic fluid every 24 hours for 5 days (6 mL)	Reduces inflammation and fibrosis	Single group, open label, pilot study; 10 participants	NA	<ul style="list-style-type: none"> ▶ Ventilator-free days. ▶ Duration of supplemental oxygen use. 	Early phase I	Ongoing
10.	Preclinical study	PneumoBlast cell therapy	PneumoBlast cell therapy: fibroblast-based cell therapy/dose: NR	'Universal donor' fibroblasts: produces potent anti-inflammatory protein IL-1 receptor antagonist: prevent scar tissue	NR	Bone marrow derived mesenchymal stem cells	<ul style="list-style-type: none"> ▶ Reduced lung fibrosis by 51% in a bleomycin model of lung scarring in mice. ▶ PneumoBlast: 221% more effective than bone marrow derived mesenchymal stem cells. 	Preclinical	Completed

DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution CT; IL-1, interleukin 1; NA, not available; NR, not reported; RCT, Randomised controlled trial.

for post-COVID-19 weakness and muscle pain; however, early rehabilitation programme can help in recovery of the muscular strength in these patients.

REHABILITATION

Rehabilitation often has an important role to play in combating persistent fatigue and physical deconditioning and tends to improve the overall quality of life. Rehabilitation includes a holistic and multidisciplinary approach towards patients involving management of secretions, respiratory muscle training, upper and lower limb exercises as well as counselling and education regarding future prospects.⁸⁶ In severe cases requiring invasive mechanical ventilation, rehabilitation can start as early as when the patient is on the ventilator to improve outcomes. Patients with milder symptoms might be advised for remote rehabilitation, while severe cases can be considered for institutional rehabilitation. Cardio-pulmonary rehabilitation tends to have a role in recovery period and in acute phase. It is seen that rehabilitation when started in mild patients during the acute phase with the aim of improving

patient's performance status at time of discharge tends to show positive effect on exercise capacity and mental function of the patients. It is important to identify the high-risk patients and start rehabilitation early and should be part of standard of care.⁸⁸

IMPLICATIONS

Post-COVID-19 syndrome is an entity that should be actively looked into as it is associated with a significant social and economic burden for the family and the healthcare system. Most of the healthcare system worldwide are already overburdened by this deadly pandemic and hence an additional cost of post-COVID-19 care will further deplete the resources. India, one of the developing nations, is now emerging as a global hotspot for COVID-19 with already 8.7 million confirmed cases and 8.1 million recovered cases.⁸⁹ Extrapolating the data of 10% of recovered patients having persistent symptoms (UK study) to the Indian context, the number of patients with post-COVID-19 syndrome would amount to nearly 0.81 million, a number huge enough to overburden the healthcare. Assuming a \$10 expenditure per patient for post-COVID-19 care (including hospital visits, investigations and medications), it would amount to 8.1 million dollars of additional expenditure for the healthcare system. In addition, a poor quality of life and absenteeism from work due to feeling unwell would further lead to loss of productive work hours compounding the economic losses. This calls for greater awareness and prompt management for post-COVID-19 syndrome lest the damage would be too huge to be undone.

CONCLUSION

Little is known about the postdischarge course of patients with COVID-19 and the long-term complications. It is still not clear whether the persistent fatigue and dyspnoea are related to pulmonary sequelae or are subsequent to non-pulmonary causes such as arrhythmias or heart failure. There is a need for systematic evaluation of patients recovering from COVID-19 infection in order to better understand their healthcare needs. It often leads to significant morbidity, and the optimal management strategies still remains unclear. In the past 9 months, noteworthy efforts have been made to understand the pathophysiology of the disease; however, post-COVID-19 sequelae is still in its infancy. A host of studies are under way to evaluate the natural history of the disease including its long-term sequelae and to identify individuals at greatest risk of post-COVID-19 syndrome.

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Main messages

- ⇒ This article reviews the entire spectrum of post-COVID-19 sequelae including involvement of the various organ systems.
- ⇒ We give a detailed insight into the epidemiology, pathophysiology and clinical manifestations including multisystem involvement, diagnosis and management.
- ⇒ We have also highlighted the implications of post-COVID-19 syndrome especially in the context of developing countries like India.

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Self-assessment questions

- ⇒ Multisystem involvement is seen COVID-19 infection.
- ⇒ Chronic fatigue is commonly seen postacute viral infections.
- ⇒ Post-COVID-19 stroke is only seen in young individuals.
- ⇒ Thromboprophylaxis is recommended in all patients post-COVID-19 infection.
- ⇒ Vaccination is an effective strategy to tackle COVID-19 pandemic.

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Answers

1. True.
2. True.
3. False.
4. False.
5. True.