

# Long COVID: “And the fire rages on”

*Awatansh Kumar Rajkumar Tripathi, Lancelot Mark Pinto*

*P.D.Hinduja National Hospital and Medical Research Centre, Mumbai, Maharashtra, India*

## ABSTRACT

With the increasing cohort of COVID-19 survivors worldwide, we now realize the proportionate rise in post-COVID-19 syndrome. In this review article, we try to define, summarize, and classify this syndrome systematically. This would help clinicians to identify and manage this condition more efficiently. We propose a tool kit that might be useful in recording follow-up data of COVID-19 survivors.

**KEY WORDS:** Long COVID, long hauler, post-COVID complications, post-COVID fibrosis, post-COVID sequelae, post-COVID syndrome

**Address for correspondence:** Dr. Lancelot Mark Pinto, P.D.Hinduja National Hospital and Medical Research Centre, Mumbai, Maharashtra, India.  
E-mail: lance.pinto@gmail.com

**Submitted:** 19-Dec-2020

**Revised:** 26-Feb-2021

**Accepted:** 24-Jun-2021

**Published:** 26-Oct-2021

## INTRODUCTION

The first case of COVID-19 in India was reported on January 31, 2020. Since then, most of the resources (financial, political, medical research, health infrastructure, etc.) have been primarily focused on arresting the spread of the disease and treating patients with the disease, i.e. interventions at primary and secondary care level. With these strategies, India has presently achieved over 90% recovery.<sup>[1]</sup> 9.5 million cases recovered out of 10 million reported as of December 19, 2020.<sup>[2]</sup> However as the cohort of survivors expands, it is now being realized that a parallel epidemic of the post-COVID syndrome/long COVID is emerging. This can be regarded as a syndrome encompassing the chronic noncommunicable, often debilitating sequelae of COVID-19. The available literature suggests that up to 88% of COVID-19 survivors may have this syndrome. Understanding the causes, natural history, and how best to intervene are all crucial to the management of the syndrome and will help the health-care system gear up to provide tertiary prevention that may be needed as a consequence.

## WHAT IS POST-COVID SYNDROME?

It can be defined as a constellation of symptoms due to the involvement of various body systems in COVID patients after the active phase of the disease has settled.

A postviral syndrome after a respiratory viral infection has been reported during previous pandemics. However, unlike the present pandemic, its burden on community health was not large enough to draw attention. The magnitude of such postviral complications was highlighted in one of the longest follow-up studies in 71 health-care workers (HCWs) affected during the first severe acute respiratory syndrome-coronavirus (SARS-CoV) pandemic.<sup>[3]</sup> These patients were followed for 15 years to observe the incidence of pulmonary and systemic complications. Residual radiological changes were seen in around 9% of the patients, a majority of which improved in a year and remained static thereafter. Pulmonary dysfunction was seen in around 36% of patients, while necrosis of the femoral head was seen in 32% of the

Access this article online	
<b>Quick Response Code:</b> 	<b>Website:</b> www.lungindia.com
	<b>DOI:</b> 10.4103/lungindia.lungindia_980_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Rajkumar Tripathi AK, Pinto LM. Long COVID: “And the fire rages on”. Lung India 2021;38:564-70.

survivors due to the use of high-dose steroids. Similarly, the incidence of pulmonary fibrosis was reported to be 38%–50% post-SARS CoV-1, 33% with MERS (Middle East Respiratory Syndrome), 10% with swine flu (H1N1), and 19% with avian flu (H7N9). However, the progression of pulmonary fibrosis was relatively uncommon with SARS, H1N1, and H7N9 whereas 13% progression was reported with host mass pulmonary fibrosis.<sup>[4-8]</sup> The post-COVID syndrome encompasses multiple organ systems. A summary of the organ systems involved can be found in Table 1. The discussion will focus on the various organ systems, clinical manifestations, and sequelae that have been reported in the past year of the pandemic.

## PULMONARY SEQUELAE

Pulmonary sequelae of COVID-19 include persistent symptoms, residual radiographic changes, and impairment in pulmonary function.

### Persistent symptoms

In a study done in Italy, 143 COVID-19 survivors were followed up for an average of 2 months. It was found that close to 43% of these patients had persistent dyspnea, which after fatigue (reported by 53% of these patients), was the most common persisting symptom.<sup>[9]</sup> Similar results were replicated in various studies which observed survivors for 4 weeks–3 months. This duration of symptom persistence is greater than what has been reported among those who recover from community-acquired pneumonia.<sup>[10,11]</sup>

**Table 1: Summary of post-COVID sequelae**

Pulmonary sequelae
Persistent dyspnea
Chronic cough and nonspecific chest pain
Persistent radiographic changes (mainly GGOs and fibrosis)
Pulmonary function impairment (mainly DL <sub>CO</sub> )
Neuromuscular sequelae
Headache, myalgia, and fatigue (most common)
Anosmia
Ageusia
Hot flushes
Neurofocal deficit postischemic stroke
Meningoencephalitis, acute necrotizing encephalopathy, acute disseminated encephalomyelitis, Guillain-Barre syndrome, and acute flaccid paralysis (scattered case reports)
Neuropsychiatric sequelae
Anxiety
Posttraumatic stress disorder
Depression
Brain fog, delirium, and hallucinations
Cardiovascular and metabolic sequelae
Arrhythmia
Venous-thromboembolism
Dyslipidemia and impaired glucose tolerance
Gastrointestinal, hepatic, and renal sequelae
Anorexia, diarrhea, and nausea/vomiting
Persistent viral shedding
Transaminitis
Increased fecal calprotectin
Acute kidney injury and chronic kidney diseases

GGOs: Ground-glass opacities, DL<sub>CO</sub>: Diffusion capacity of the lung

### Residual radiographic abnormalities

In a retrospective multicenter study from China, 55 COVID-19 survivors were followed for 3-month postdischarge. This study reported radiographic abnormalities in about 71% of individuals.<sup>[11]</sup> There have been case reports of new-onset bronchiectasis and organizing pneumonia among COVID-19 survivors.<sup>[12,13]</sup>

### Residual pulmonary dysfunction

In another cross-sectional analysis, done in 110 COVID survivors, an abnormal diffusion capacity of the lung (DL<sub>CO</sub>) was reported in 47% of individuals.<sup>[14]</sup> There was a decline in DL<sub>CO</sub> even when adjusted for alveolar volume (DL<sub>CO</sub>/V<sub>A</sub>), suggesting that the loss of diffusion capacity was out of proportion to the loss of vital capacity. Systemic corticosteroids used in moderate-severe COVID-19 pneumonia are known to cause muscle atrophy. Besides, infection with SARS-CoV-2 is now recognized as an independent cause of respiratory muscle strength impairment. In a Chinese study, 49.1% and 22.8% had P<sub>i</sub> max and P<sub>e</sub> max values <80% of the predicted value independent of the use of corticosteroids.<sup>[15]</sup>

These findings suggest that a large proportion of recovered COVID-19 patients will need pulmonary rehabilitation and close follow-up.<sup>[16]</sup> The posthospitalization COVID-19 study (PHOSP-COVID) conducted by a consortium of leading researchers and clinicians from across the UK is recruiting patients to create an evidence base for long COVID. COVID-19 survivors with a residual pulmonary impairment will be followed up for at least 36 months to assess the clinical course of the disease.<sup>[16]</sup> Table 2 below summarizes the key studies done among post-COVID-19 patients.<sup>[9,17-21]</sup>

## CARDIOVASCULAR SEQUELAE

The incidence of myocardial injury during active COVID-19 infection has been reported to be 14%–19%.<sup>[22,23]</sup> Various mechanisms have been postulated such as direct myocardial injury, downregulation of angiotensin-converting enzyme 2 (ACE2) receptors severe inflammation, and hypoxic damage secondary to severe SARS-CoV-2 pneumonia.<sup>[24,25]</sup> However, such post-COVID myocardial dysfunction does not appear to be limited to severely infected patients. A cohort of 100 individuals who had recovered from COVID-19 was followed at University Hospital Frankfurt in Germany.<sup>[26]</sup> Most of these patients (67%) were presymptomatic and were treated at home, and none of them had a history of previous cardiac illness. At an average of 71 days, the incidence of cardiac anomalies as evident on cardiac magnetic resonance imaging was 78%, while active myocardial inflammation was present in 60% of the patients. Arrhythmias have also been reported and are a cause of concern.

Metabolic abnormalities dyslipidemia and impaired glucose metabolism are relatively common months after

**Table 2: Summary of key studies on post-COVID syndrome**

Study	Sample size	Follow-up period (days)	Fatigue (%)	Dyspnea (%)	Cough (%)	Chest pain (%)	Number of patients with at least one symptom (%)	Remark
Carfi <i>et al.</i> , 2020 <sup>[9]</sup>	143 (included critical patients)	60	53	43	18	21	87 (123)	Fatigue most common symptom
Carvalho-Schneider <i>et al.</i> , 2021 <sup>[17]</sup>	150 noncritical patients	60	40 (52)	30 (39)	-	16 (9)	66 (86)	Anosmia/ageusia: 59%
Garrigues <i>et al.</i> , 2020 <sup>[18]</sup>	120 (included 24 ICU)	110	55 (66)	42 (50)	16 (20)	11 (13)	-	Fatigue most common symptom 30% sleep disorder 34% memory loss
Halpin <i>et al.</i> , 2020 <sup>[19]</sup>	100 (included 32 ICU)	Up-to 70	72 and 60 (ICU and non-ICU group)	65 and 42	30 and 15	-	-	Incidence of PTSD was twice in ICU patients (50%)
Tenforde <i>et al.</i> , 2020 <sup>[20]</sup>	274 (out patients)	Up-to 41	35	29	43	-	65	93% of this patients were nonhospitalized
Huang <i>et al.</i> , 2021 <sup>[21]</sup>	1733 (included critical patients)	186	63	26	-	5	76	Fatigue most common symptom

ICU: Intensive care unit, PTSD: Posttraumatic stress disorder

discharge, caused by direct effects of disease and adverse effects of corticosteroids used during treatment.<sup>[25]</sup>

Hypercoagulability is well recognized in COVID-19 patients.<sup>[27]</sup> A serum d-dimer level has been identified as one of the important predictors of adverse outcomes among hospitalized patients with COVID-19.<sup>[28]</sup> SARS-CoV-2-induced coagulopathy is postulated to be due to ACE2 receptor-mediated endotheliitis, hypoxia-induced lung injury, cytokine-mediated hemophagocytic lymphohistiocytosis-like syndrome,<sup>[29]</sup> and neutrophil extracellular trap.<sup>[29]</sup> These pathophysiological changes can have long-term implications in COVID-19 survivors. Around 60% of recovered patients are at high risk of developing venous thromboembolic events (VTEs) up to 90 days after discharge,<sup>[30]</sup> odds ratio (OR) of hospital-associated – VTE within 42-day postdischarge has been reported as high as 1.6,<sup>[31]</sup> while the incidence of symptomatic VTEs can be as high as 0.6%.<sup>[32,33]</sup> The current guidelines recommend continuing thromboprophylaxis up to 45 after discharge.<sup>[34]</sup>

## NEUROPSYCHIATRIC SEQUELAE

The uncertainty and unpredictability in the natural history of the disease, discrimination and stigmatization associated with the diagnosis, adverse effects of social isolation, and influence of an atmosphere of fear created by lockdowns and reporting of the illness in the media have possibly contributed to an increase in the incidence of psychiatric illness among COVID survivors.<sup>[34,35]</sup> The burden of corticosteroid-induced neuropsychiatric effects in the current pandemic has not been quantified. The previous SARS epidemic resulted in an incidence as high as 0.7%.<sup>[36]</sup> HCWs have been at a high risk of developing psychiatric illnesses. The burden of psychiatric illness on HCW was studied in a systematic review and meta-analysis, which included 13 cross-sectional studies comprising 33,062 HCW with post-COVID status. It found that incident anxiety, depression, and posttraumatic stress disorder were reported in up to 20%–25% HCWs,

with the highest prevalence among females and nursing staff.<sup>[37]</sup> In a survey led by a patient on a digital platform, a significant proportion of individuals who had recovered from COVID had persistent symptoms, which were independent of the severity of the illness.<sup>[38]</sup> Symptoms reported included "brain fog," hallucinations, delirium, short-term memory loss, and strange vibration sense. The pathophysiology of these symptoms remained unexplained. There are various postulated mechanisms proposed to explain these symptoms, one of which has been offered by Akiko Iwasaki, an immunologist at Yale.<sup>[39]</sup> According to this postulate, a patient may have latent virus or fragments of its genetic material in various body tissues postrecovery. These latent particles may cause a persistent immune activation, or an immunological reactivation responsible for the symptoms. Another postulate by David Putrino, Director of rehabilitation innovation at Mount Sinai suggests that patients with long COVID develop neurological dysautonomia, which could affect up to 15% of all COVID-19 survivors.<sup>[40]</sup> However, these hypotheses are still to be validated by studies.

## NEUROLOGICAL SEQUELAE

Post-COVID-19 neurological syndrome encompasses all the neurological disorders that are observed in the convalescence phase of COVID-19 infection. Neurotropism of coronaviruses has been previously demonstrated in various studies.<sup>[41,42]</sup> The clinical features associated with novel coronavirus-19 infection are consistent with the previous observation that such viruses have a broad spectrum of neurological presentations. Headaches, anosmia, meningoencephalitis, acute ischemic stroke, several post/para-infectious syndromes, and psychiatric disorder are neurotropic symptoms independent of primary respiratory pathophysiology.<sup>[43]</sup> The most common proposed mode of central nervous system penetration is through the olfactory bulb during the early stages and through blood during the phase of viremia.<sup>[44]</sup> Persistent anosmia is one of the most common post-COVID symptoms which is caused by the

injury to the olfactory bulb, rich in ACE2 receptor, the binding site of the virus. Various hypotheses have been postulated to explain the pathophysiology of neurological injury, most of them emphasizing the hypercoagulable state in COVID-19 patients, which increases the risk of acute ischemic stroke. In addition, in some of the animal model studies done in past, coronaviruses have been demonstrated to cause demyelination postintracerebral administration.<sup>[45]</sup> The phenomenon of molecular mimicry between coronaviruses and myelin sheath<sup>[46,47]</sup> can cause T-cell-mediated cross-reactivity, and subsequent autoimmune disease, even after viral clearance. A follow-up study was conducted among 2113 COVID-19 recovered patients, most of whom (2001 out of 2113) were not hospitalized and were mildly symptomatic. After an average of 71 days from illness onset, the incidence of self-reported headache was 76%, muscular pain 64%, ageusia 42%, anosmia 40%, and hot flushes in 25% of patients.<sup>[10]</sup> Apart from these manifestations, case reports are highlighting severe and morbid neurological outcomes in COVID patients such as meningoencephalitis, acute necrotizing encephalopathy, acute disseminated encephalomyelitis, and acute flaccid paralysis.<sup>[43]</sup> More recently neurologists in the city of Mumbai have reported 24 cases of Guillain–Barre syndrome and few cases of Bell’s palsy in COVID survivors.<sup>[48,49]</sup> This disturbing observation is still to be evaluated for its temporal and causal relationship with active COVID-19 infection. The presentation of COVID-19 with cerebrovascular accidents has been described fairly commonly,<sup>[50,51]</sup> and the consequent residual neurodeficits and psychological effects of such loss of function would also be part of the sequelae of the disease that we are likely to face often.

## GASTROINTESTINAL AND HEPATIC SEQUELAE

Coronaviruses affecting the gastrointestinal (GI) tract are common. In the studies, evaluating the incidence of GI symptoms in MERS-CoV-infected patients, diarrhea was reported in 12%–23%, vomiting in 21%–33%, and abdominal pain in 27%–40% of patients.<sup>[52,53]</sup> In a recent meta-analysis including 4243 COVID patients from 60 studies, the pooled prevalence of GI symptoms was 17.6%. Anorexia was the most common symptom followed by nausea/vomiting and diarrhea. Stool samples were positive for viral RNA in 48% of patients of which one-third of the samples were collected after respiratory samples were tested negative.<sup>[54]</sup> This persistence of fecal viral shedding in COVID patients has been correlated with high levels of fecal calprotectin (up to 80% of patients with GI symptoms) caused by injury to GI epithelium which is rich in ACE2 receptor.<sup>[55]</sup> Similarly, liver injury among COVID-19 patients with GI symptoms can be as high as 17%.<sup>[56]</sup> These patients may have a high risk for an adverse disease outcome and are not eligible for the administration of remdesvir, which is the only antiviral drug with some evidence on efficacy against COVID-19.<sup>[57]</sup>

## RENAL SEQUELAE

In a recent meta-analysis, the pooled estimate of the prevalence of acute kidney injury (AKI) in patients with severe COVID-19 was 28%.<sup>[58]</sup> The development of AKI is an indicator for a high mortality OR of death being as high as 9%.<sup>[59]</sup> The estimated OR for the incidence of AKI in deceased versus survivor COVID-19 patients is 15.4.<sup>[58]</sup> Renal disease related to COVID-19 can also manifest up to 6-month postdischarge in patients who had no kidney injury during the active phase of viral infection. In a cohort study that followed up, 1733 COVID-19 patients for an average of 186-day postdischarge found 107 patients with no AKI, and normal estimated glomerular filtration rate (eGFR) during the acute phase had eGFR <90 mL/min/1.73 m<sup>2</sup> at follow-up.<sup>[21]</sup> Autopsy studies have concluded that acute tubular necrosis is the most common mode of renal injury followed by nonspecific infiltration.<sup>[60,61]</sup> The proposed mechanisms for the development of AKI in COVID patients are hypoxemia and hypercapnia, hypotension, endothelitis, rhabdomyolysis, and direct viral injury.

## TREATMENT

Suggesting treatment for long COVID in the absence of understanding the natural history of the disease would be unscientific, and patients should be enrolled in clinical trials when feasible. For example, the role of antifibrotic medications for post-COVID fibrosis is being investigated.<sup>[62]</sup> Screening for (and consequently treating) underlying cardiac and lung disease, metabolic abnormalities, vitamin deficiencies, electrolyte imbalances, hormonal dysregulation would all be part of optimizing the recovery process.

Physiotherapy, including pulmonary rehabilitation<sup>[63]</sup> when indicated, along with dietary modifications should not be ignored. In the absence of any large trials for pulmonary rehabilitation for post-COVID states, it would be prudent to follow the guidelines for pulmonary rehabilitation in other lung diseases that manifest with fibrotic interstitial.<sup>[64,65]</sup> The principles of rehabilitation would include exercise training (both resistance and aerobic), energy conservation techniques, dietary and lifestyle changes, with a structured approach to ensure adherence and incremental gains. Facilitating smoking cessation, screening for obstructive sleep apnea, and treating it would also be part of rehabilitating individuals for long COVID.

## THE WAY FORWARD

Several lacunae in the knowledge and understanding of long COVID still exist: we do not yet know whether long COVID manifestations are attributable to the virus or a dysregulated immune system. The long-term trajectory of these effects remains unknown, as does the probability of

success of interventions attempting to alter the course. The first step toward understanding any disease is collecting data to understand the natural history of the disease and attempting to understand predictors of severity. With this aim, all recovered patients must be followed up after their initial illness, and protocols for doing so have been published.<sup>[16,66-68]</sup> Follow-up can be virtual on a digital platform or in-person as per the social restrictions and patient’s comfort. We propose a simple and comprehensive tool kit [Table 3] for post-COVID-19 follow-up assessment. Such a toolkit is intended to be a framework to cover the most commonly reported symptoms. However, one may need to add more questions to cover other domains (such as sleep) or may need to contextualize this to the local lexicon (“weakness” vs. “fatigue” vs. “lack of energy” vs. “feeling low”).

## CONCLUSION

A review of the available literature makes it evident that of those who survived COVID-19 illness; a significant proportion (nearly 60%–80%) is likely to experience a post-COVID syndrome up to 6 months after the active infective illness. Despite SARS-CoV-2 predominantly being a respiratory pathogen and COVID-19 a respiratory pandemic, post-COVID effects among survivors encompass a broad spectrum. This spectrum includes pulmonary, cardiovascular, neuromuscular, neuropsychiatric systems, and some yet-understood atypical features. It is also important for clinicians to keep in mind that the severity and duration of post-COVID symptoms may not necessarily correlate with the severity of the acute COVID illness.

Individuals who present with features of long COVID must be followed up closely and enrolled in longitudinal studies

**Table 3: Toolkit for follow-up of COVID-19 patients**

History of COVID illness
WHO severity of infection (mild, moderate, or severe)
Total hospital stay (including ward stay and intensive care unit)
Maximum oxygen required and mode of delivery
Dose and days corticosteroid steroid administered
Other treatment received
Any other complications
Status at discharge
Questionnaire for follow-up at 1 <sup>st</sup> month
mMRC dyspnea grading
PCFS <sup>[64]</sup>
HADS <sup>[66]</sup>
History suggestive of any persistent or new symptoms such as fever, fatigue, cough, palpitations
Investigations for follow-up at 1 <sup>st</sup> month
Resting oxygen saturation, 6-min walk test
Spirometry, single-breath diffusion capacity, lung volumes
Comprehensive metabolic panel, D-dimer, NT-pro-BNP, electrocardiogram
SARS-CoV-2 antibody
Chest HRCT

NT-pro-BNP: N-Terminal proB-type natriuretic peptide, PCFS: Post-COVID-19 functional status, HADS: Hospital Anxiety and Depression Scale, mMRC: Modified medical research council, HRCT: High-resolution computed tomography, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

so that we can better comprehend the disease and conduct research on potential therapies to its natural history. Toolkits, which cover the commonly reported symptoms, and can be modified to local contexts could be invaluable.

As the number of patients with the disease continues to rise, we must do our best to not only just focus on hospitalizations and treatment but also focus on an increasingly reported incidence of long COVID.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Health Ministry Says India’s Covid-19 Recovery Rate among Highest Globally, Active Cases Fall Further-Health-Hindustan Times. Available from: <https://www.hindustantimes.com/health/health-ministry-says-india-s-covid-19-recovery-rate-among-highest-globally-active-cases-fall-further/story-Uf4k9K81V1AZ5YhHMY7deL.html>. WLast accessed on 2020 Dec 18].
2. Coronavirus Outbreak in India. Available from: <https://www.covid19india.org/>. [Last accessed on 2020 Dec 19].
3. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: A 15-year follow-up from a prospective cohort study. *Bone Res* 2020;8:8.
4. Das K, Lee E, Singh R, Enani M, Al Dossari K, Van Gorkom K, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. *Indian J Radiol Imaging* 2017;27:342.
5. Li P, Zhang JF, Xia XD, Su DJ, Liu BL, Zhao DL, et al. Serial evaluation of high-resolution CT findings in patients with pneumonia in novel swine-origin influenza A (H1N1) virus infection. *Br J Radiol* 2012;85:729-35.
6. Toufen C, Costa EL, Hirota AS, Li HY, Amato MB, Carvalho CR. Follow-up after acute respiratory distress syndrome caused by influenza A (H1N1) virus infection. *Clinics* 2011;66:933-7.
7. Singh N, Singh S, Sharma BB, Singh V. Swine flu fibrosis: Regressive or progressive? *Lung India* 2016;33:219-21.
8. Wang Q, Jiang H, Xie Y, Zhang T, Liu S, Wu S, et al. Long-term clinical prognosis of human infections with avian influenza A (H7N9) viruses in China after hospitalization. *EclinicalMedicine* 2020;20:100282.
9. Carli A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *J Am Med Assoc* 2020;324:603-5.
10. Goertz YM, Van Herck M, Delbressine JM, Vaes AW, Meys R, Machado FV, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: The post-COVID-19 syndrome? *ERJ Open Res* 2020;6:00542-2020.
11. Halpin SJ, Mclvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2021;93:1013–22. doi: 10.1002/jmv.26368.
12. Vadász I, Husain-Syed F, Dorfmüller P, Roller FC, Tello K, Hecker M, et al. Severe organising pneumonia following COVID-19. *Thorax* 2021;76:201-4.
13. Ambrosetti MC, Battocchio G, Zamboni GA, Fava C, Tacconelli E, Mansueto G. Rapid onset of bronchiectasis in COVID-19 pneumonia: Two cases studied with CT. *Radiol Case Rep* 2020;15:2098-103.
14. Mo X, Jian W, Su Z, Chen M, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J* 2020;55:2001217. doi: 10.1183/13993003.01217-2020.
15. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res* 2020;21:163.
16. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: Monitoring the clinical course in survivors. *Lancet Respir Med* 2020;8:839-42.
17. Carvalho-Schneider C, Laurent E, Lemaigen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical

- COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;27:258-63.
18. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020;81:e4-6.
  19. Halpin SJ, Mclvor C, Whyatt G, Adams A, Harvey O, McLean L, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. *J Med Virol* 2020;93:jmv. 26368. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26368>. [Last accessed on 2020 Nov 20].
  20. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network – United States, March–June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:993-8.
  21. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-Month consequences of COVID-19 in patients discharged from hospital: A cohort study. *Lancet* 2021;397:220-32.
  22. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
  23. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;5:802-10.
  24. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, et al. ST-segment elevation in patients with Covid-19 – A case series. *N Engl J Med* 2020;382:2478-80. doi: 10.1056/NEJMc2009020.
  25. Capotosto L, Nguyen BL, Ciardi MR, Mastroianni C, Vitarelli A. Heart, COVID-19, and echocardiography. *Echocardiography* 2020;37:1454-64.
  26. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1265-73. doi: 10.1001/jamacardio.2020.3557. Available from: <https://jamanetwork.com/>. [Last accessed on 2020 Oct 23].
  27. Kumar A, Narayan RK, Kumari C, Faiq MA, Kulandhasamy M, Kant K, et al. SARS-CoV-2 cell entry receptor ACE2 mediated endothelial dysfunction leads to vascular thrombosis in COVID-19 patients. *Med Hypotheses* 2020;145:110320.
  28. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020;18:1324-9. doi: 10.1111/jth.14859.
  29. Zuo Y, Zuo M, Yalavarthi S, Gockman K, Madison JA, Shi H, et al. Neutrophil extracellular traps and thrombosis in COVID-19. *J Thromb Thrombolysis* 2021;51:446-53. doi: 10.1007/s11239-020-02324-z.
  30. Wise J. Covid-19 and thrombosis: What do we know about the risks and treatment? *BMJ* 2020;369:m2058.
  31. Roberts LN, Whyte MB, Georgiou L, Giron G, Czuprynska J, Rea C, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. *Blood* 2020;136:1347-50.
  32. COVID-19 and VTE-Anticoagulation. Available from: <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>. [Last accessed on 2020 Oct 23].
  33. Flaczyk A, Rosovsky RP, Reed CT, Bankhead-Kendall BK, Bittner EA, Chang MG. Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: Implications for clinical practice and future investigations. *Crit Care* 2020;24:559.
  34. Bao Y, Sun Y, Meng S, Shi J, Lu L. 2019-nCoV epidemic: Address mental health care to empower society. *Lancet* 2020;395:e37-8.
  35. Ozamiz-Etxebarria N, Dosal-Santamaria M, Picaza-Gorrochategui M, Idoiaga-Mondragon N. Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. *Cad Saude Publica* 2020;36:e00054020.
  36. Lee DT, Wing YK, Leung HC, Sung JJ, Ng YK, Yiu GC, et al. Factors associated with psychosis among patients with severe acute respiratory syndrome: A case-control study. *Clin Infect Dis* 2004;39:1247-9.
  37. Pappa S, Ntella V, Giannakas T, Giannakoulis VG, Papoutsis E, Katsaounou P. Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis. *Brain Behav Immun* 2020;88:901-7.
  38. COVID-19 Prolonged Symptoms Survey-Analysis Report-Google Docs. Available from: [https://docs.google.com/document/d/1KmLkOArIjem-PAMbM5pS\\_E3OozD47UzvRG4qM5Yk/edit#](https://docs.google.com/document/d/1KmLkOArIjem-PAMbM5pS_E3OozD47UzvRG4qM5Yk/edit#). [Last accessed on 2020 Nov 20].
  39. Thousands of COVID-19 Long-haulers Are Still Sick - The Atlantic. Available from: <https://www.theatlantic.com/health/archive/2020/06/covid-19-coronavirus-longterm-symptoms-months/612679/>. [LAsT accessed on 2021 Jul 18].
  40. Why Do "Mild" Covid-19 Cases Sometimes Linger for Months? Here's What Experts Say. Available from: <https://www.advisory.com/daily-briefing/2020/07/27/long-term-covid>. [Last accessed on 2020 Nov 20].
  41. Li YC, Bai WZ, Hirano N, Hayashida T, Hashikawa T. Coronavirus infection of rat dorsal root ganglia: Ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. *Virus Res* 2012;163:628-35.
  42. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020;92:552-5.
  43. Khateb M, Bosak N, Muqary M. Coronaviruses and central nervous system manifestations. *Front Neurol* 2020;11:715.
  44. Toljan K. Letter to the Editor regarding the viewpoint "Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanism". *ACS Chem Neurosci* 2020;11:1192-4.
  45. Fleming JO, Trousdale MD, Bradbury J, Stohlman SA, Weiner LP. Experimental demyelination induced by coronavirus JHM (MHV-4): Molecular identification of a viral determinant of paralytic disease. *Microb Pathog* 1987;3:9-20.
  46. Talbot PJ, Paquette JS, Ciurli C, Antel JP, Ouellet F. Myelin basic protein and human coronavirus 229E cross-reactive T cells in multiple sclerosis. *Ann Neurol* 1996;39:233-40.
  47. Boucher A, Desforges M, Duquette P, Talbot PJ. Long-term human coronavirus-myelin cross-reactive T-cell clones derived from multiple sclerosis patients. *Clin Immunol* 2007;123:258-67.
  48. Bell's Palsy: Facial Nerve Paralysis Found in Coronavirus Patients | Cities News, The Indian Express. Available from: <https://indianexpress.com/article/cities/mumbai/bells-palsy-facial-nerve-paralysis-found-in-coronavirus-patients-7059627/>. [Last accessed on 2020 Nov 21].
  49. Mumbai Reports Over 24 Cases of Guillain-Barré Syndrome which Causes Paralysis in Recovered Covid-19 Patients-Mumbai News-Hindustan Times. Available from: <https://www.hindustantimes.com/mumbai-news/mumbai-reports-over-24-cases-of-guillain-barre-syndrome-which-causes-paralysis-in-recovered-covid-19-patients/story-pYR4gA49YJQSKbTXMWILM.html>. [Last accessed on 2020 Nov 21].
  50. Fraiman P, Godeiro C Jr., Moro E, Cavallieri F, Zedde M. COVID-19 and cerebrovascular diseases: A systematic review and perspectives for stroke management. *Front Neurol* 2020;11:574694.
  51. Dhmoon MS, Thaler A, Gururangan K, Kohli A, Sisniega D, Wheelwright D, et al. Acute cerebrovascular events with COVID-19 infection. *Stroke* 2021;52:48-56. Available from: <http://ahajournals.org>. [Last accessed on 2021 Mar 13].
  52. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: A descriptive study. *Lancet Infect Dis* 2013;13:752-61.
  53. Garbati MA, Fagbo SF, Fang VJ, Skakni L, Joseph M, Wani TA, et al. A comparative study of clinical presentation and risk factors for adverse outcome in patients hospitalised with acute respiratory disease due to MERS coronavirus or other causes. *PLoS One* 2016;11:e0165978.
  54. Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. *Gastroenterology* 2020;159:81-95.
  55. Jena A, Kumar MP, Singh AK, Sharma V. Fecal calprotectin levels in COVID-19: Lessons from a systematic review on its use in inflammatory bowel disease during the pandemic. *Dig Liver Dis* 2020;53:295.
  56. Ye Q, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *Am J Physiol Gastrointest Liver Physiol* 2020;319:G245-52.
  57. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 – Final report. *N Engl J Med* 2020;383:1813-26.
  58. Silver SA, Beaubien-Souligny W, Shah PS, Harel S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 infection: A systematic review and meta-analysis. *Kidney Med*

- 2021;3:83-98.e1.
59. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S, *et al.* AKI in hospitalized patients with COVID-19. *J Am Soc Nephrol* 2021;32:151-60.
  60. Santoriello D, Khairallah P, Bomback AS, Xu K, Kudose S, Batal I, *et al.* Postmortem kidney pathology findings in patients with COVID-19. *J Am Soc Nephrol* 2020;31:2158-67.
  61. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, *et al.* Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020;98:219-27.
  62. Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis-Full Text View. Available from: <https://clinicaltrials.gov/ct2/show/NCT04541680>. [Last accessed on 2021 Mar 13].
  63. Zhu Y, Wang Z, Zhou Y, Onoda K, Maruyama H, Hu C, *et al.* Summary of respiratory rehabilitation and physical therapy guidelines for patients with COVID-19 based on recommendations of World Confederation for Physical Therapy and National Association of Physical Therapy. *J Phys Ther Sci* 2020;32:545-9.
  64. Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. *Cochrane Database Syst Rev* 2014;(10):CD006322. doi: 10.1002/14651858.CD006322.pub3.
  65. Nakazawa A, Cox NS, Holland AE. Current best practice in rehabilitation in interstitial lung disease. *Ther Adv Respir Dis* 2017;11:115-28.
  66. Klok FA, Boon GJ, Barco S, Endres M, Geelhoed JJ, Knauss S, *et al.* The post-COVID-19 Functional Status scale: A tool to measure functional status over time after COVID-19. *Eur Respir J* 2020;56(1):2001494.
  67. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020;370:m3026. Available from: <http://dx.doi.org/10.1136/bmj.m3026>. [Last accessed on 2020 Dec 18].
  68. Gupta S, Prasad AS, Dixit PK, Padmakumari P, Gupta S, Abhisheka K. Survey of prevalence of anxiety and depressive symptoms among 1124 healthcare workers during the coronavirus disease 2019 pandemic across India. *Med J Armed Forces India* 2020. doi: 10.1016/j.mjafi.2020.07.006. [Epub ahead of print].