



Post COVID-19 Syndrome: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author AK designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors AM and APM managed the analyses of the study. Author SK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The COVID-19 pandemic shook the entire world in January 2020 last year and is still posing a major threat to the entire humanity. A lot of studies have been conducted studying the diagnosis and management of the disease caused by this highly contagious virus, but less is known about the Post COVID-19 sequelae. There is very limited evidence about the management of COVID-19 after the first three weeks of illness. About 10% of the patients experience prolonged illness after COVID-19. Treatment is mainly focused on reassurance, self-care, and symptomatic control. There are currently no FDA-approved treatments specifically for this condition. Clinicians and researchers have focused on the acute phase of COVID-19, but continued monitoring after discharge for long-lasting effects is needed.

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1. INTRODUCTION

Even though the number of COVID-19 cases worldwide now approaches 87 million with more than 1.8 million dead, we know very little about this complex and evolving disease. The disease is highly infectious, has wide clinical spectrum and there are no proven antiviral drugs so far [1,2]. Early in the pandemic, many people believed that COVID-19 was a short-term illness. World Health Organization (WHO) in February 2020, using preliminary data available at the time, reported the time from onset to clinical recovery for mild cases was approximately 2 weeks and that recovery took 3 to 6 weeks for patients with the severe or critical disease. More recently, however, it has become clear that in some patients debilitating symptoms persist for weeks or even months. In some of these patients, symptoms have never gone away [3]. Experience with Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), post-acute respiratory distress syndrome complications and post-intensive care syndrome has taught us the clinical profile and anticipated sequelae. But the natural history of post-acute and chronic COVID-19 in a community population is unknown at the time of writing this article. Here the study review the current knowledge of post COVID-19, using the term "Post COVID-19 Syndrome".

2. DEFINITION

There is no agreed definition of Post-COVID-19 Syndrome so far. Greenhalgh et al, have defined Post-acute COVID-19 as extending beyond 3 weeks from the onset of first symptoms and Post-chronic COVID-19 as extending beyond 12 weeks [4]. A positive test for COVID-19 is not a prerequisite for diagnosis since many people are not tested, and false-negative tests are common [5,6]. Other terminologies have included "long COVID," "post-COVID syndrome" and "post-acute COVID-19 syndrome." Among the lay public, the phrase "long haulers" is also being used. Without a formally accepted definition of Post COVID-19 syndrome, it is difficult to assess how common it is, how long it lasts, who's at risk for it, what causes it, what its pathophysiology is, and how to treat and prevent it [7].

3. PREVALENCE

So far as COVID-19 is concerned, up to 40% of people infected never develop symptoms. Out of

the rest 60% symptomatic patients, about 80% have a mild illness that does not require hospitalization; about 15% are sick enough to require hospitalization; and only 5% require care in an intensive care unit, usually for mechanical ventilation to treat respiratory insufficiency [8].

The exact prevalence of Post-acute and Post-chronic COVID-19 Syndrome is not known. In a smartphone-based study in UK (UK COVID Symptom Study), it was found that around 10% of the patients who had tested positive for SARS-CoV-2 virus, remain unwell beyond 3 weeks, and a smaller proportion for months [9]. This percentage is lower than that cited in many published observational studies, where populations were those admitted to hospital or attending specialist clinics. A recent US study found that only 65% of people had returned to their previous level of health 14-21 days after a positive test [10].

4. PATHOPHYSIOLOGY

Although much has been discovered regarding the transmission and presentation, relatively little is known about the associated morphologic and molecular changes in the peripheral lung of patients who die from COVID-19. In 1976 Katzenstein et al. had described the histological hallmark of the early phase of ARDS as diffuse alveolar damage, edema, hemorrhage, and intra-alveolar fibrin deposition [11]. Broadly, the Post-COVID-19 syndrome patients can be divided into acute, those who may have serious sequelae such as thromboembolic complications and chronic, those with a non-specific clinical picture, often dominated by fatigue and breathlessness [12].

Maximilian et al. [13] in a study of 7 patients, who died from COVID-19, studied the lungs samples with the use of seven-color immunohistochemical analysis, micro-computed tomographic imaging, scanning electron microscopy, corrosion casting, direct multiplexed measurement of gene expression, and found that the lungs showed distinctive vascular features, consisting of severe endothelitis, associated with the presence of intracellular virus and disrupted cell membranes. The pulmonary vessels showed widespread thrombosis with microangiopathy and intussusceptive angiogenesis.

Neutrophil extracellular traps (NETs) release (NETosis) is a powerful mechanism of microbial

destruction whereby neutrophils die and release digestive granules containing neutrophil elastase (NE) and myeloperoxidase (MPO). The concomitant and inflammatory release of auto-antigens from dying neutrophils is increasingly a hallmark of autoimmune processes. As foreseen, NETosis participates in several tissue-specific and systemic autoimmune diseases like systemic lupus erythematosus, antineutrophil cytoplasmic antibodies (ANCA) vasculitis, rheumatoid arthritis, antiphospholipid syndrome and multiple sclerosis [14].

If NETosis is confirmed as the leading cause of severe and fatal evolution of COVID-19 as several research teams envision, one must be prepared to observe a resurgence of a non-infectious inflammatory illness among convalescents: the "Post COVID-19 Syndrome" [15].

The question is that if indeed COVID-19 is causing long-term sequelae, then are the mechanisms underlying the long-term consequences immunological or caused by new or relapsing inflammation, ongoing infection, or side effects of immunomodulatory treatment [16].

5. INVESTIGATIONS

A complete blood count (CBC) should be done in all post-COVID-19 patients as anaemia can present as breathlessness, alterations in white cell count in infection or inflammatory response and lymphopenia being a feature of severe acute COVID-19. Elevated biomarkers include C reactive protein (in acute infection), ferritin (inflammation and continuing prothrombotic state), D-dimer (thromboembolic disease), troponin (acute coronary syndrome or myocarditis) and natriuretic peptides (for example, heart failure). Troponin and D-dimer tests may be falsely positive, but a negative result can reduce clinical uncertainty. A chest X-ray at 12 weeks should be advised for patients who have had a significant respiratory illness. A HRCT chest for progressive symptoms or new, persistent, abnormal chest x ray should be done. Patients should be tested for antinuclear antibodies and the tests repeated after 6 weeks, especially if they are young women with rheumatologic pain, in order to rule out a possible dormant underlying autoimmune disease [17]. The role of a pulmonary function test though not defined can be done for initial assessment and subsequent follow-up as it is affordable and can be done at bedside.

Self-monitoring of oxygen saturations over three to five days may be useful in patients with persistent dyspnea in the post-acute phase. In absence of contraindications, a six minute walk test should be performed as part of the baseline assessment. A fall of 3% in the saturation reading on mild exertion is abnormal and requires investigation [18].

Overall, patients with persistent symptoms, beyond 8 weeks after the onset of COVID-19 should be tested with COVID-19 serology, echocardiography and MRI heart to rule out another diagnosis, especially myopericarditis. Investigations in the post-acute phase should include an endocrine screen and a DEXA scan for decreased bone mineral density (BMD).

6. CLINICAL FEATURES

In a telephone survey of 274 symptomatic RT-PCR positive COVID-19 non-hospitalized adults, about one third reported not having returned to their usual state of health 2 to 3 weeks after testing [19]. In another phone-based survey of 120 COVID-19 discharged patients Carfi et al. [20] observed the most common reported symptoms being dyspnea (42%), memory loss (34%), sleep disorders (30.8%) and difficulty with concentration (28). In Italy in a study of 143 patients after about a 2-week-hospitalization for COVID-19, many patients still struggled with symptoms 60 days on average after onset of their illness; 87% still had at least one symptom, particularly fatigue and dyspnea and 55% had 3 or more symptoms. In France, more and more Post-COVID-19 patients experienced anosmia and ageusia, followed by a short period of convalescence. Subsequently, they complained of relapse with persistent symptoms, especially myalgia, intense fatigue, sensation of fever, shortness of breath, chest tightness, tachycardia, headaches and anxiety [21].

The reported symptoms are usually due to the affection of respiratory tract, neurological, cardiovascular, gastrointestinal, and various other systems. The top ten symptoms, reported by 70% or more respondents include shortness of breath, tightness of the chest, fatigue, chills or sweats, body aches, dry cough, fever, headache, and brain fog or difficulty in concentration. About 70% had been physically fit before the onset of symptoms, but 70% reported being sedentary after the onset of symptoms [22].

The pulmonary lesions associated with COVID-19 can cause chronic long-lasting lung disease. Her cough has been seen to persist beyond eight weeks. A degree of breathlessness is common after acute COVID-19. Severe breathlessness is rare in patients who were not hospitalized. Breathlessness tends to improve with breathing exercises [23].

Most of these lesions will gradually heal or disappear, but some of them will develop pulmonary fibrosis which causes shortness of breath and limits the ability to be physically active. The cardiac complications include myocarditis, pericarditis, myocardial infarction, heart failure, arrhythmias and pulmonary embolus. Palpitation is the commonest symptom. They are common in patients with pre-existing cardiovascular disease, but they have also been described in young, previously active patients. Perhaps 20% of patients admitted with COVID-19 have clinically significant cardiac involvement. In an observational cohort study, 78 of 100 patients who had recovered from COVID-19 had abnormal findings on cardiovascular MRI (median of 71 days after diagnosis) and 36 of those reported dyspnea and unusual fatigue [24].

At present when the COVID-19 pandemic is going on, there is an emerging evidence of a new syndrome, Post COVID-19 neurological Syndrome (PCNS) with prolonged muscle weakness and other forms of myopathy among COVID-19 survivors in Hongkong [25]. The first case of Guillain-Barre Syndrome (GBS) following COVID-19 was reported by Duranii et al as a post-infectious complication but subsequently, there is increasing recognition of a link between COVID-19 and GBS, with eight published cases associated with COVID-19 (a case series of five patients from Italy and a single case report from China, Iran and USA) [26]. A case of infectious acute transverse myelitis (ATM) attributed to SARS-CoV-2 in a 24-year-old male who presented with bilateral lower-extremity weakness and overflow urinary incontinence has been reported [27]. Also, cases of Kawasaki-like multisystem inflammatory syndromes (MIS) are being recognized in children and teenagers. Evidence strongly suggests that patients surviving COVID-19 are at high risk for subsequent development of neurological disease and in particular Alzheimer's disease [28].

The long-term endocrine and metabolic complications of COVID-19 include increased risk of hyperglycemia, dyslipidemia, hypo

cortisolism and primary or central hypothyroidism. The psychiatric impact of COVID-19 has been associated with varying degrees of depression, sleep impairment and anxiety. In a study on 714 COVID-19 patients in China, nearly 97% of the patients were displaying symptoms of severe post-traumatic stress disorder (PTSD). Peter et al have reported a case of orthostatic hypo perfusion syndrome (OCHOS), a form of orthostatic intolerance and painful small fiber neuropathy (SFN) in a 64-year-old lady illustrating a case of a post-infectious autonomic syndrome likely due to autoimmune process in patient with previous COVID-19 disease [29].

Persistent musculoskeletal aches and pains, reactive arthritis (symmetric arthritis of large joints) rheumatoid arthritis-like presentation (arthritis of the small joints) and femoral head necrosis are some of the presentations of post COVID-19 syndrome. Post viral chronic fatigue syndrome, similar to fibromyalgia, with poor sleep, fatigue, myalgia and depression with some unable to return to work, as a result, are also seen.

Post-intensive care syndrome (PICS) is described in severely ill COVID-19 patients who have recovered after a prolonged ICU stay is due to persistent inflammation, immunosuppression and catabolism syndrome. Substantial cardiovascular morbidity and mortality accompany PICS, even in young and fit populations without traditional cardiovascular risk factors [30]. The risks of COVID-19 to all voice users are substantial. For some singers, these post-COVID-19 conditions may seem worse than dying itself. As shocking as this sentiment may seem, musicians in one study who had lost the ability to play their instrument due to injury described the emotional effects as "drastic," "traumatic" and "devastating." One musician stated, "It was almost like my life had stopped" while another simply explained, "music's my life." [31].

7. MANAGEMENT

Management of post COVID-19 Syndrome is currently based on limited experiences; as many such patients recover spontaneously, if slowly with holistic support, rest, symptomatic treatment and gradual increase inactivity. In US 65% of people had returned to their previous level of health 14-21 days after a positive test. Approximately 10% of people experienced

prolonged illness after COVID-19. There is much debate and controversy about the role of graded exercise in chronic fatigue syndrome. Pending direct evidence from research studies, it is suggested that exercise in such patients should be undertaken cautiously and cut back if the patient develops fever, breathlessness, severe fatigue or muscle aches. Chronic cough may persist for more than eight weeks and unless there are signs of super-infection or other complications such as painful pleural inflammation, cough seems to be best managed with simple breathing control exercises. Fatigue in post COVID-19 can be managed by quality rest, relaxation, establishing good sleep routines, to find a balance between rest and activity and not pushing beyond physical limits.

It may be that early intervention and supportive treatments at the end of the acute phase of COVID-19 can help overcome acute phase symptoms and prevent them from becoming longer-term consequences [32-34]. In those who have hyperglycemia, sick day rules, which involve increased monitoring of blood sugar and ketones, remaining hydrated and fed, increasing insulin as required, and amending other diabetic medication on specialist advice, should be employed if anyone with diabetes develops COVID-19.

8. CONCLUSION

The number of people affected by COVID-19 is unprecedented. After recovering from the initial infection from COVID-19 some patients present with symptoms like extreme breathlessness, fatigue, foggy brain, palpitations and memory loss. Recent analysis by the COVID Symptom Study suggested that as many as one in 10 people with COVID-19 have been sick for more than three weeks after symptoms first emerged. Treatment is mainly focused on reassurance, self-care and symptomatic control. There are currently no FDA-approved treatments specifically for this condition. Clinicians and researchers have focused on the acute phase of COVID-19, but continued monitoring after discharge for long-lasting effects is needed. Healthcare planners and policymakers must prepare to meet the needs of the many people that have been affected by this illness and their families while ongoing studies investigate causes and ways to mitigate the post-COVID syndrome. Global clinical registries with a meticulous systems-based approach to the assessment, management and reporting of post-

COVID patients will aid in the exploration of the key clinical features of COVID-19 disease as well as the efficacy of potential interventions in the coming months.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gupta P, Mohanty A, Narula H, Singh V, Kalita D, Varshney S et al. Concise Information for the Frontline Health care workers in the era of COVID-19- A Review. *Indian J Comm Health*. 2020;32(2):215-224.
2. Kabi A, Mohanty A, Mohanty AP, Vijalaxmi, Kumar N, Kumar S. Medical management of COVID-19: treatment options under consideration. *Int J Adv Med* 2020;7:1603-11.
3. Geddes L. Why strange and debilitating coronavirus symptoms can last for months. *New Scientist*. 2020. Available:<https://www.newscientist.com/article/mg24632881-400-why-strange-and-debilitatingcoronavirus-symptoms-can-last-for-months/>
4. Ray Perrin, Lisa Riste, Mark Hann. *Medical Hypotheses*; 2020. Available:<https://doi.org/10.1016/j.mehy.2020.110055>.
5. Mohanty A, Kabi A, Mohanty A P, Kumar N, Kumar S. Laboratory diagnosis of COVID-19 infection: Issues and Challenges: An Indian Perspective. *Journal of Advances in Medicine and Medical Research*. 2020;32(14):10-17.
6. Mohanty A, Kabi A, Kumar S, Hada V. Role of rapid antigen test in the diagnosis of COVID-19 in India. *Journal of Advances in Medicine and Medical Research* 2020; 32(18):77-80.
7. Trisha Greenhalgh, Matthew Knight, Christine A'Court, Maria Buxton, Laiba HMusain. Management of post-acute

- covid-19 in primary care. *BMJ* 2020; 370:m3026.
DOI: 10.1136/bmj.m3026.
8. Assaf G, Davis H, McCorkell L et al. An analysis of the prolonged COVID-19 symptoms survey by Patient-Led Research Team. *Patient Led Research*; 2020. Available:<https://patientresearchcovid19.com/>.
 9. COVID Symptom Study. How long does COVID-19 last? Kings College London, 2020. Available:https://covid19.joinzoe.com/post/covid-long-term?fbclid=IwAR1RxlcmmdL-EFjh_al-
 10. Tenforde MW, Kim SS, Lindsell CJ, 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.
 11. Worldometer; 2020. Available:<https://www.worldometers.info/coronavirus/>
 12. Katzenstein AL, Bloor CM, Leibow AA. Diffuse alveolar damage—the role of oxygen, shock, and related factors. A review. *Am J Pathol.* 1976;85(1):209-28. PMID: 788524; PMCID: PMC2032554.
 13. Phillips M, Turner-Stokes L, Wade D et al. Rehabilitation in the wake of Covid-19—A phoenix from the ashes. *British Society of Rehabilitation Medicine*; 2020. Available:<https://www.bsrm.org.uk/downloads/covid-19bsrmissue1-published-27-4-2020.pdf>.
 14. Maximilian Ackermann, Stijn E. Verleden, Mark Kuehnel, Axel Haverich, Tobias Welte et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020; 383:120-8.
 15. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol.* 2018;18(2):134-147. DOI: 10.1038/nri.2017.105. Epub 2017 Oct 9. PMID: 28990587.
 16. Tomar B, Anders HJ, Desai J, Mulay SR. Neutrophils and neutrophil extracellular traps drive necroinflammation in COVID-19. *Cells.* 2020;9. Available:<https://doi.org/10.3390/cells9061383>.
 17. Dana Yelin, Eytan Wirtheim, Pauline Vetter, Andre C Kalil, Judith Bruchfeld et al. Long-term consequences of COVID-19: Research needs. *Lancet.* 2020;20:1115-17.
 18. British Thoracic Society. British thoracic society guidance on respiratory follow up of patients with a clinico-radiological diagnosis of COVID-19 pneumonia; 2020. Available:<https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/resp-follow-up-guidance-post-covidpneumonia/>.
 19. Greenhalgh T, Javid B, Knight M et al. What is the efficacy and safety of rapid exercise tests for exertional desaturation in covid-19? *Oxford COVID-19 Evidence Service*; 2020. Available:<https://www.cebm.net/covid-19/what-is-the-efficacy-and-safety-of-rapid-exercise-tests-for-exertional-desaturation-in-covid-19/>
 20. Tenforde MW, Kim SS, Lindsell CJ et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multi-state health care systems network-United States, MMWR. 2020;69:993-998. Available:https://www.cdc.gov/mmwr/volumes/69/wr/mm6930e1.htm?s_cid=mm6930e1_e&deliveryName=USCDC_921-DM33740
 21. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603–605.
 22. Benjamin Davido, Sophie Seang, Roland Tubiana, Pierre de Truchis. Post-COVID-19 chronic symptoms: A postinfectious entity? *Clinical Microbiology and Infection.* 2020. Available:<https://doi.org/10.1016/j.cmi.2020.07.028>.
 23. Carfi A, Bernabei R, Landi F. For the gemelli against COVID-19 post-acute care study group. Persistent Symptoms in Patients after Acute COVID-19. *JAMA.* 2020;324(6):603–605. DOI:10.1001/jama.2020.12603
 24. Hull JH, Lloyd JK, Cooper BG. Lung function testing in the COVID-19 endemic. *Lancet Respir Med.* 2020;8:666-7.
 25. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*; 2020. Available:<https://doi.org/10.1001/jamacardio.2020.3557>.

26. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); A novel syndrome with challenges for the global neurology community Journal of the Neurological Sciences. 2020;419:117179.
27. Muhammad Durrani, Kevin Kucharski, Zachary Smith, Stephanie Fien, PA. Clin Pract Cases Emerg Med. 2020;4(3):344–348.
28. Toscano G, Palmerini F, Dm RS, et al. Guillain–Barré syndrome associated with SARS-CoV-2. N Engl J Med. 2020;4.
29. Heneka MT, Golenbock D, Latz E et al. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. Alz Res Therapy. 2020;12:(69). Available:https://doi.org/10.1186/s13195-020-00640-3
30. Peter Novak. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: A case report. eNeurological Sci. 2020;21: 100276.
31. Mansoor Bangash N, Andrew Owen, Joseph Alderman E, Minesh Chotalia, Jaimin Patel M, Dhruv Parekh. COVID-19 recovery: Potential treatments for post-intensive care syndrome. 2020;8. Available:www.thelancet.com/respiratory
32. Zaza Christine, Charles Cathy, Muszynski Alicja. The meaning of playing-related musculoskeletal disorders to classical musicians. Soc Sci Med. 1998;47:2013–2023.
33. Barua M, Kumar S, Mishra V, Mohanty A, Joshi HS. Unmasking N95 for COVID-19 health-care workers in India. J Family Med Prim Care. 2020;9:5850-2.
34. Mohanty A, Singh TS, Bhutia TO, Gupta P, Gupta P. A case of albendazole and niclosamide resistant Taenia saginata infection. Int J Res Med Sci. 2017;5:2821-3.

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