A Review of Respiratory Post-Acute Sequelae of COVID-19 (PASC) and the Potential Benefits of Pulmonary Rehabilitation

MICHAEL SIMON, MD; JAMES E. SIMMONS, MD

ABSTRACT

With the SARS-CoV-2 pandemic continuing into its third year, the number of patients who survive acute COVID-19 infection but go on to develop long-term symptoms is increasing daily. Those individuals who experience one or more of a variety of persistent symptoms post-COVID-19 are now diagnosed with the syndrome called post-acute sequelae of COVID-19 (PASC), often colloquially called "Long COVID." This article discusses relevant research and current hypotheses regarding the pathophysiology and management of respiratory symptoms of PASC, in order to provide primary care physicians with context for management of this heterogeneous population. We focus on the growing body of research that supports the use of pulmonary rehabilitation for patients with PASC to improve symptoms and quality of life.

KEYWORDS: post-acute sequelae of COVID-19; PASC; Long COVID; pulmonary rehabilitation

INTRODUCTION

COVID-19 is the disease caused by the SARS-CoV-2 virus, which was first identified in December 2019 in China.[1] The subsequent pandemic has had an immeasurable impact on humanity and claimed the lives of over 6 million people. The majority of patients infected with SARS-CoV-2 (up to 80%) will only experience mild acute disease, but still roughly 10% to 35% of these patients, as well as up to 86% of patients with moderate to severe acute COVID-19, will develop various long-term symptoms.[1-3] This syndrome is now termed post-acute sequelae of COVID-19 (PASC) and is also known colloquially as "Long COVID." We will review the current definitions and pathophysiologic understanding of PASC and then discuss the diagnostic and management strategies for people suffering with respiratory symptoms.

POST-ACUTE SEQUELAE OF COVID-19 (PASC)

More than two years since the discovery of SARS-CoV-2, we are only beginning to understand its long-term effects. With each passing variant and subsequent wave of infections, the number of patients who shift from acute infection to the post-acute syndrome increases. Though far from complete, the literature is beginning to coalesce around a definition for stratifying patients with persistent symptoms after the acute COVID-19 infection has resolved. Symptoms continuing beyond four weeks from the onset of COVID-19 are considered to be post-acute COVID-19.[4] When symptoms persist, the Centers for Disease Control and Prevention (CDC) define PASC as occurring in "individuals with a history of probable or confirmed SARS CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis."[5] Many patients with severe acute COVID-19 requiring supplemental oxygen, hospitalization, or even mechanical ventilation are unsurprisingly burdened with long-term symptoms, but PASC can also be seen in patients who were never hospitalized for acute COVID-19 and had only mild symptoms initially. Symptoms of PASC vary significantly in quality, severity, and organ system involvement. Dyspnea is the most common respiratory complaint, occurring in 15% of non-hospitalized patients and up to 81% of hospitalized patients.[6] Other commonly cited respiratory complaints include cough, chest pain, or decreased exercise tolerance.[6-8] Non-respiratory symptoms include low-grade fevers, headaches, neurocognitive difficulty, muscle pain and weakness, gastrointestinal symptoms, rashes, thromboembolic conditions, depression, and post-traumatic stress disorder. In a study of non-hospitalized post-COVID-19 patients from Germany, 30% had at least one symptom (anosmia, ageusia, fatigue, or dyspnea) at four months.[9] Beyond the known negative impact on quality of life (QOL) metrics, PASC presents an ongoing challenge for the public health system of this country.[10-12]

Although some post-acute symptoms can likely be attributed to the effects of the virus, other long-term symptoms are less clear. For example, it is well established that acute COVID-19 results in a pro-thrombotic state as compared to other viral illnesses, and resultant pulmonary emboli can lead to significant post-COVID breathlessness. The more insidious symptoms of fatigue, deconditioning, "brain fog," and psychiatric sequelae are not as well understood. The burden of disease is not only a consequence of somatic complaints, but also a decline in overall QOL.[11] There are several hypotheses for why these downstream disorders occur. Some have suggested that the deconditioning is

partially a result of immune system suppression or overreaction.[13] Specifically, there is evidence that infection by SARS-CoV-2 may cause an exaggerated host immune response that results in an extended period of auto-antibody production.[14]

The pathophysiology and inflammatory underpinnings for PASC remain unclear. There are well established post-infectious syndromes caused by other viruses and bacteria, but they vary greatly as to the underlying cause. Coronavirus infections can have long-lasting effects, including lung disease, despite a mild illness.[15] Several recent publications have attempted to elucidate the likely culprits for PASC, with varying degrees of success.[12,14,16]

The viral tropism of SARS-CoV-2, or more simply the number of different cell types it can infect, lends credence to the idea that the post-acute phase of infection affects multiple systems.[14] Specifically, SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2), which functions as a receptor, in order to enter cells; this protein is expressed not just in the entire human respiratory system but also in the brain, gastrointestinal tract, and pancreatic beta-cells.[17] Other hypotheses include residual organ damage, remaining viral reservoirs, and the possible confounding variable of post-critical illness (especially myopathy and neuropathy) for those who required intensive care.[16] In all, it is likely there are multiple pathways that lead to PASC, as broadly defined, and future studies should focus on delineating subgroups of PASC for diagnostic and management purposes.

RISK FACTORS FOR PASC

With such a broad definition and varied clinical picture for PASC, primary care physicians (PCPs) must have a low threshold to consider PASC in patients after COVID-19 infection, regardless of the initial severity and especially when there are identifiable risk factors. Much of the literature to date has focused on the chronic sequelae following severe COVID-19 infection, which have proposed pathophysiologic origins supported by prior known mechanisms of acute respiratory distress syndrome.[18] Of particular interest to primary care physicians are the impact and long-term consequences of mild or even asymptomatic COVID-19 infection. In a systematic review of patients who experienced a mild infection in the outpatient setting across Europe and the United States, between 10% and 35% of these patients still had symptoms after the acute phase of illness.[2] Furthermore, in one of the largest studies included in this comprehensive review, less than 1% of patients reported being symptom-free at three months.[2]

Clearly, PASC can occur in anyone following COVID-19, and although establishing a comprehensive list of risk factors for developing PASC will likely require years of additional study, the current literature describes some clear associations. Smoking status, elevated body mass index, cancer, older age, and pre-existing chronic respiratory disease are all associated with worse acute outcomes as well as long-term sequelae.[14,19,20] However, it is unclear how they factor into the prognostication of patients who experienced initial mild versus severe disease. In a recent systematic review and meta-analysis, a significant association was found between female sex and any reported chronic symptom (OR 1.52; 95% CI 1.27–1.82).[20] It has been hypothesized that females may have a protective genetic milieu against COVID-19 that is on the X chromosome, so that men are more likely to succumb to the acute illness and not develop long-term consequences.[16] Diabetes mellitus type 2, a high COVID viral RNA load, Epstein-Barr virus reactivation, and certain investigational autoantibodies are additionally implicated as possible risk factors.[16] In fact, in this study there was an association between particular autoantibody patterns and specific PASC symptoms. Patients with elevated levels of the IFN-alpha2 antibody were uniquely associated with respiratory symptoms of PASC, even after correcting for other factors. This may lead to the development of biomarkers that could guide the clinical management of PASC.

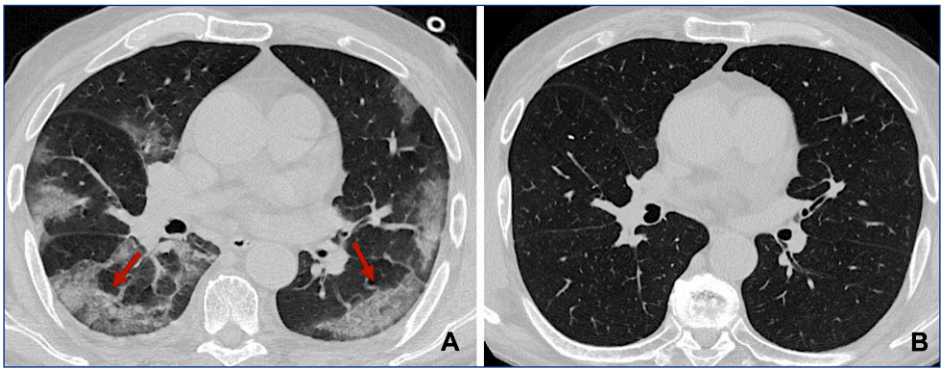
RESPIRATORY SEQUELAE

While the burden of symptoms from PASC should be appreciated through a multisystem lens, the most disabling problems in PASC are fatigue and breathlessness, so the remainder of this article will focus on these aspects and the importance of pulmonary rehabilitation.[21]

The respiratory symptoms of patients with PASC are varied, and there is emerging evidence of at least two clinical subgroups that may benefit from different management strategies. The first is characterized by fibrotic lung changes that are visible on imaging and a restrictive pattern on pulmonary function testing (PFTs), with or without diffusion capacity impairment (like the patient in **Figure 1**). The other subgroup has more acute inflammatory findings on radiography, with potentially reversible damage that may be steroid-responsive.[23,24] These cases are similar to the chronic disease seen after the first SARS virus outbreak, Middle East respiratory syndrome (MERS), and H1N1 influenza.[22] Current evidence suggests that only some patients in either group have persistent physiologic or radiographic changes that can help guide therapy. Conversely, the burden of symptoms does not always correlate to these standard measures of pulmonary function, as seen in many patients with severe respiratory symptoms of PASC who have normal PFTs and lung imaging.[23] This makes it clear that management decisions must be individualized for PASC patients.

Currently, it appears that most patients will have a slow improvement of respiratory PASC, and although the rate can vary dramatically between weeks to months, a majority have symptom resolution three months after the diagnosis of PASC.[25] Although a systematic review of respiratory function in post-acute COVID-19 found that diffusion capacity

Figure 1. Baseline and Six-month Follow-up Chest CT after Acute COVID-19 infection
Baseline and six-month follow-up axial thin-section unenhanced chest CT images in an 83-year-old man, a former smoker, who presented with fever, cough, and worsening dyspnea. COVID-19 was confirmed by using reverse transcription polymerase chain reaction testing. (**A**) The baseline image shows multiple bilateral and confluent ground-glass opacities with a predominantly linear pattern and a peripheral distribution (arrows). (**B**) The six-month follow-up image shows complete resolution of ground-glass opacities without fibrosis-like changes.



Source: Caruso D, Guido G, Zerunian M, et al. Post-Acute Sequelae of COVID-19 Pneumonia: Six-month Chest CT Follow-up. *Radiology* 2021;301:E396–E405.
(Permission to use granted by The Radiological Society of North America (RSNA®))

was abnormal in 39% of patients,[26] the PFT abnormalities decreased in incidence over time. This suggests that the timing of a pulmonary function testing is important to establish a new baseline as the lungs heal, though no practice pattern has been validated to this point.

RECOMMENDATIONS FOR PRIMARY CARE PHYSICIANS

Internists and family practitioners are typically the front-line physicians who manage these patients. Although we should consider PASC in post-COVID-19 patients, it is also important to remember the new axiom that "all that appears long-haul is not COVID." A reasonable workup to rule out confounding, concomitant, or alternative diagnoses distinct from PASC should be undertaken to evaluate persistent symptoms following COVID-19 infection. While guidelines are scarce, there appears to be some agreement regarding evaluations for patients with respiratory symptoms of PASC. These include chest radiograph, PFTs, and six-minute walking distance (6MWD) testing at 12 weeks post-infection for baseline measurement.[27-29] Further evaluation with high resolution computed tomography (HRCT) or echocardiography following evidence of residual infiltrates on chest radiograph should be done in association with referral to appropriate specialists.[27-29]

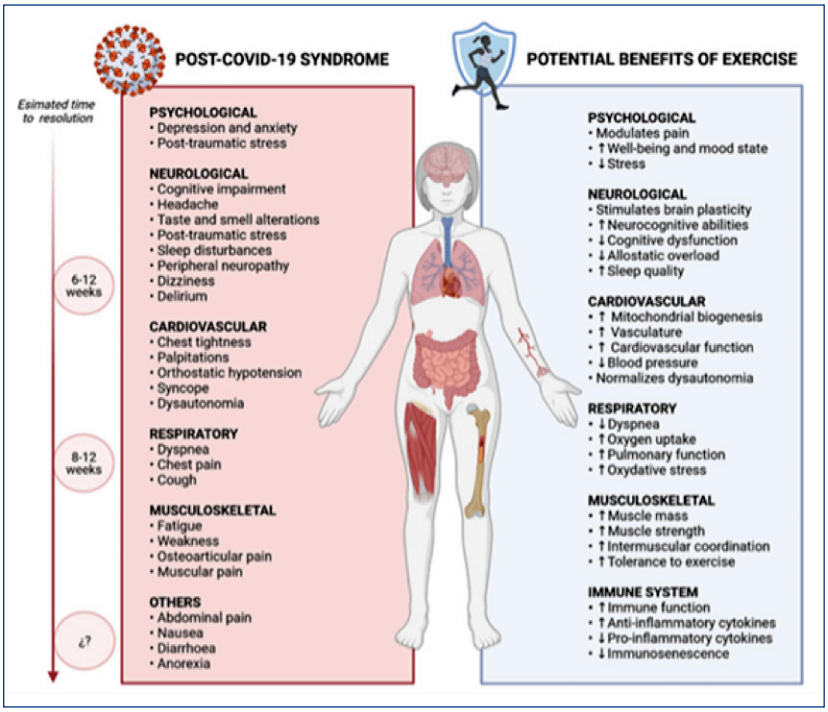
Supplemental oxygen should be prescribed to patients who have resting or exertional hypoxemia (generally oxygen saturation <88%) as in other chronic lung diseases; many patients do improve their DLCO, so the need for oxygen should be re-evaluated after two to three months. The diagnostic and therapeutic management of chronic lung disease following COVID-19 is beyond the scope of this article, as there is not yet consensus on many of the difficult clinical decisions that arise for these patients. This speaks to the broader consensus that an interdisciplinary care model is likely to be most beneficial. In that context, if patients have radiographic or PFT abnormalities that correlate to respiratory symptoms or a patient requires supplemental oxygen, then it is reasonable to involve a pulmonologist to determine the need for medical therapies such as systemic steroids for possible inflammatory lung disease, bronchodilators for airways disease, or evaluation for neuromuscular disease.

PULMONARY REHABILITATION

Pulmonary rehabilitation (PR) has emerged as a safe and effective intervention that can be offered to patients with shortness of breath lasting four weeks after confirmed or suspected COVID-19 infection; Medicare covers reimbursement for this indication. PR is defined as "a multidisciplinary intervention based on personalized evaluation and treatment which includes, but is not limited to, exercise training, education, and behavioral modification designed to improve the physical and psychological condition of people with respiratory disease."[30]

In our two years of caring for PASC patients in The Miriam Hospital Center for Cardiac, Pulmonary and Vascular Fitness PR program, we have seen many remarkable cases of significant improvement in QOL measures and dyspnea scores after our 12-week program. This includes two visits a week for individualized and monitored exercise as well as interdisciplinary interventions such as a COVID support group and psychosocial supports. Past patients have included those who were treated for acute respiratory distress related to COVID-19 in an intensive care unit for weeks and survived with chronic supplemental oxygen and tracheostomies, but there are also many previously healthy young patients with mild to moderate acute COVID-19. One such patient was a 40-year-old female marathon runner who developed such significant dyspnea on exertion that she could barely walk across the room despite normal oxygen requirements, PFTs, and chest imaging. Both types of patients had significant improvements in their dyspnea, their QOL based on standard PR measures, and exercise tolerance as measured by 6MWD, despite likely different

Figure 2. Potential Benefits of Exercise on the Most Frequent Clinical Manifestations of post-COVID-19 syndrome



Source: Jimeno-Almazán A, Pallarés JG, Buendía-Romero Á, Martínez-Cava A, Franco-López F, Sánchez-Alcaraz Martínez BJ, Bernal-Morel E, Courel-Ibáñez J. Post-COVID-19 Syndrome and the Potential Benefits of Exercise. Int J Environ Res Public Health. 2021 May 17;18(10):5329. doi: 10.3390/ijerph18105329. PMID: 34067776; PMCID: PMC8156194. https://pubmed.ncbi.nlm.nih.gov/34067776/

pathophysiologic mechanisms. Anecdotally, overall adverse events for these PASC patients do not appear significantly different from the other chronic lung disease patients we have managed for years.

Our experience has been confirmed by mounting scientific evidence that PR is beneficial for PASC patients with respiratory symptoms. While there has not been an established minimal clinical important difference (MCID) for improvement of 6MWD in survivors of COVID-19, the studies in a meta-analysis by Chen et al surpassed the accepted 30 meters for MCID in other chronic lung disease. Specifically, the pooled estimate of improvement was 50.41 meters--despite some studies not including endurance training, which may underestimate the true impact of pulmonary rehabilitation.[31] In another study, patients with mild to moderate COVID-19 infection were able to increase 6MWD by 47 meters, despite PR occurring six months after the initial infection.[32] This encouraging finding supports the benefit of rehabilitation in parallel with the natural recovery process, even if the infection was fairly remote. More recent studies have built on this finding with an impressive number needed to treat of 1.26 to achieve a one-grade improvement in a post-COVID-19 functional status scale.[33] There are many mechanisms by which PR may benefit these patients with more than just their respiratory complaints, as described in **Figure 2**.

While the SARS-CoV-2 virus will likely become endemic in our microbiologic ecosystem, we continue to grapple with the consequences of the pandemic. Encouragingly, the respiratory symptoms of PASC show the promise of improvement through pulmonary rehabilitation. With each passing day, the number of COVID survivors increases, and even though a significant number will suffer from long-term consequences of the infection, we also gain new insights into the diagnosis and management of PASC through the ongoing efforts of researchers and clinicians globally.

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Apr 7 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648
2. van Kessel SAM, Olde Hartman TC, Lucassen P, van Jaarsveld CHM. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. Fam Pract. Jan 19 2022;39(1):159-167. doi:10.1093/fampra/cmab076
3. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. Jan 16 2021;397(10270):220-232. doi:10.1016/S0140-6736(20)32656-8
4. Montani D, Savale L, Noel N, et al. Post-acute COVID-19 syndrome. Eur Respir Rev. Mar 31 2022;31(163) doi:10.1183/16000617.0185-2021
5. Long COVID or Post-COVID Conditions. Accessed June 14, 2022, https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
6. Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. Lancet Respir Med. Jul 2021;9(7):747-754. doi:10.1016/S2213-2600(21)00174-0
7. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. Aug 2020;25:100463. doi:10.1016/j.eclinm.2020.100463
8. Bellan M, Soddu D, Balbo PE, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. JAMA Netw Open. Jan 4 2021;4(1):e2036142. doi:10.1001/jamanetworkopen.2020.36142
9. Augustin M, Schommers P, Stecher M, et al. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Health Eur. Jul 2021;6:100122. doi:10.1016/j.lanepe.2021.100122
10. Tabacof L, Tosto-Mancuso J, Wood J, et al. Post-acute COVID-19 Syndrome Negatively Impacts Physical Function, Cognitive Function, Health-Related Quality of Life, and Participation. Am J Phys Med Rehabil. Jan 1 2022;101(1):48-52. doi:10.1097/PHM.0000000000001910

11. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. J Med Virol. Jan 2022;94(1):253-262. doi:10.1002/jmv.27309
12. Menges D, Ballouz T, Anagnostopoulos A, et al. Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study. PLoS One. 2021;16(7):e0254523. doi:10.1371/journal.pone.0254523
13. Han Q, Zheng B, Daines L, Sheikh A. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. Pathogens. Feb 19 2022;11(2)doi:10.3390/pathogens11020269
14. Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. Front Microbiol. 2021;12:698169. doi:10.3389/fmicb.2021.698169
15. Zhang P, Li J, Liu H, 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. doi:10.1038/s41413-020-0084-5
16. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. Mar 3 2022;185(5):881-895 e820. doi:10.1016/j.cell.2022.01.014
17. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med. Jul 2020;26(7):1017-1032. doi:10.1038/s41591-020-0968-3
18. Nguyen NN, Hoang VT, Dao TL, Dudouet P, Eldin C, Gautret P. Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review. Eur J Clin Microbiol Infect Dis. Apr 2022;41(4):515-545. doi:10.1007/s10096-022-04417-4
19. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med. Apr 2021;27(4):626-631. doi:10.1038/s41591-021-01292-y
20. Maglietta G, Diodati F, Puntoni M, et al. Prognostic Factors for Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis. J Clin Med. Mar 11 2022;11(6)doi:10.3390/jcm11061541
21. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med. Apr 2021;27(4):601-615. doi:10.1038/s41591-021-01283-z
22. Boutou AK, Georgopoulou A, Pitsiou G, Stanopoulos I, Kontakiotis T, Kioumis I. Changes in the respiratory function of COVID-19 survivors during follow-up: A novel respiratory disorder on the rise? Int J Clin Pract. Oct 2021;75(10):e14301. doi:10.1111/ijcp.14301
23. Myall KJ, Mukherjee B, Castanheira AM, et al. Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment. Ann Am Thorac Soc. May 2021;18(5):799-806. doi:10.1513/AnnalsATS.202008-1002OC
24. Boutou AK, Asimakos A, Kortianou E, Vogiatzis I, Tzouvelekis A. Long COVID-19 Pulmonary Sequelae and Management Considerations. J Pers Med. Aug 26 2021;11(9)doi:10.3390/jpm11090838
25. Jiang DH, Roy DJ, Gu BJ, Hassett LC, McCoy RG. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. Sep-Oct 2021;6(9):796-811. doi:10.1016/j.jacbts.2021.07.002
26. Torres-Castro R, Vasconcello-Castillo L, Alsina-Restoy X, et al. Respiratory function in patients post-infection by COVID-19: a systematic review and meta-analysis. Pulmonology. Jul-Aug 2021;27(4):328-337. doi:10.1016/j.pulmoe.2020.10.013
27. George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. Thorax. Nov 2020;75(11):1009-1016. doi:10.1136/thoraxjnl-2020-215314
28. Funke-Chambour M, Bridevaux PO, Clarenbach CF, et al. Swiss Recommendations for the Follow-Up and Treatment of Pulmonary Long COVID. *Respiration*. 2021;100(8):826-841. doi:10.1159/000517255
29. Antoniou KM, Vasarmidi E, Russell AM, et al. European Respiratory Society Statement on Long COVID-19 Follow-Up. *Eur Respir J*. Feb 10 2022;doi:10.1183/13993003.02174-2021
30. Barker-Davies RM, O'Sullivan O, Senaratne KPP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med*. Aug 2020;54(16):949-959. doi:10.1136/bjsports-2020-102596
31. Chen H, Shi H, Liu X, Sun T, Wu J, Liu Z. Effect of Pulmonary Rehabilitation for Patients With Post-COVID-19: A Systematic Review and Meta-Analysis. *Front Med (Lausanne)*. 2022;9:837420. doi:10.3389/fmed.2022.837420
32. Gloeckl R, Leitl D, Jarosch I, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. *ERJ Open Res*. Apr 2021;7(2)doi:10.1183/23120541.00108-2021
33. Nopp S, Moik F, Klok FA, et al. Outpatient Pulmonary Rehabilitation in Patients with Long COVID Improves Exercise Capacity, Functional Status, Dyspnea, Fatigue, and Quality of Life. *Respiration*. Feb 24 2022:1-9. doi:10.1159/000522118

Authors

Michael Simon, MD, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Alpert Medical School of Brown University, Providence, Rhode Island.

James E. Simmons, MD, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Alpert Medical School of Brown University, Providence, Rhode Island; The Miriam Hospital Center for Cardiac, Pulmonary and Vascular Fitness, Pulmonary Rehabilitation Program.

Disclosure

James E. Simmons, MD, is the medical director of The Miriam Hospital Center for Cardiac, Pulmonary and Vascular Fitness pulmonary rehabilitation program.

Correspondence

James E. Simmons, MD
Brown Medicine, Inc. Pulmonary Critical Care
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903
401-444-5773
Fax 401-444-6279
James_E_Simmons@brown.edu