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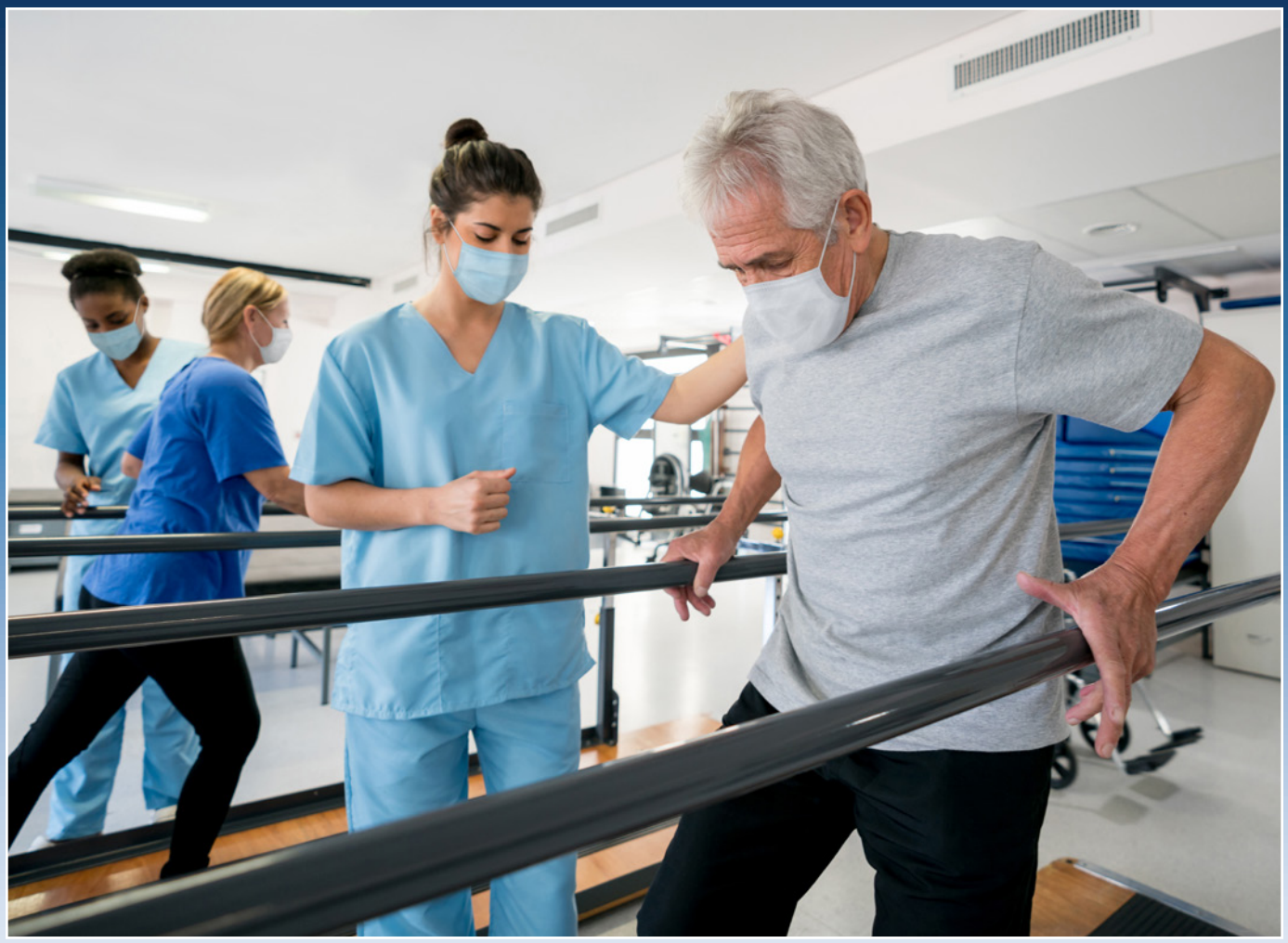


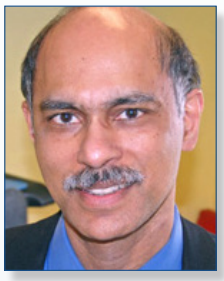
SPECIAL SECTION

EVALUATION *and* REHABILITATION *of* LONG COVID

GUEST EDITOR: JON A. MUKAND, MD, PhD

SEPTEMBER 2022 VOLUME 105 • NUMBER 7 ISSN 2327-2228

RHODE ISLAND MEDICAL JOURNAL



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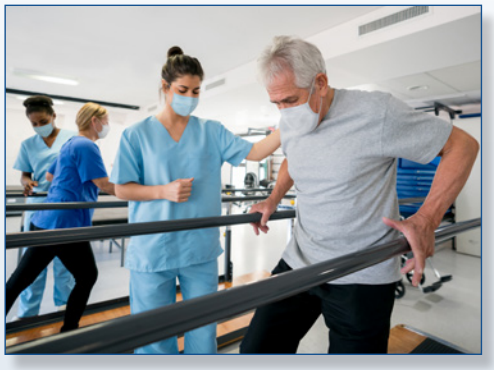


On the cover: Post-COVID patients in a rehabilitation center during a physiotherapy class. [iStock]

RIMJ Special Section: The Evaluation & Rehabilitation of Long COVID

JON A. MUKAND, MD, PhD
GUEST EDITOR

INTRODUCTION

People with COVID-19 who have "persistent symptoms, or the onset of long-term symptoms, ≥4 weeks after acute COVID-19" are contending with post-acute sequelae of SARS-CoV-2 (PASC), or Long COVID.[1] An important Centers for Disease Control and Prevention (CDC) study used a matched cohort design to search the medical records of about 1,640,000 controls and 353,000 case patients during March 2020–November 2021. The authors looked for 26 post-COVID conditions, including the pulmonary, cardiac, neurologic, gastrointestinal, renal, hematologic, and musculoskeletal systems (**Figure 1**).[2] At least one condition related to the viral infection was present in 20% of COVID-19 survivors aged 18–64 years and 25% who were ≥65 years. In the older population, the relative risk was at or more than 1.5 for pulmonary emboli, respiratory symptoms, renal failure, thromboembolic events, fatigue, acute myocardial infarction, myopathies, neurologic conditions, Type 2 diabetes, smell/taste disturbance, and cardiac dysrhythmias (listed in decreasing incidence).[2] These conditions are all linked by angiotensin converting enzyme 2 (ACE2), which acts as a functional receptor on cell surfaces for SARS-CoV-2 to invade the cells. "ACE2 expression occurs in alveolar, bronchial/respiratory, myocardial, breast, endothelial, arterial smooth muscle, tongue, esophageal, stomach, ileum, colon, rectum, renal proximal tubule, bladder, testicular, uterus, ovarian, and maternal-fetal cells as well as neurons and glia, cholangiocytes, adipose tissue, and pancreatic exocrine glands and islets."[3]

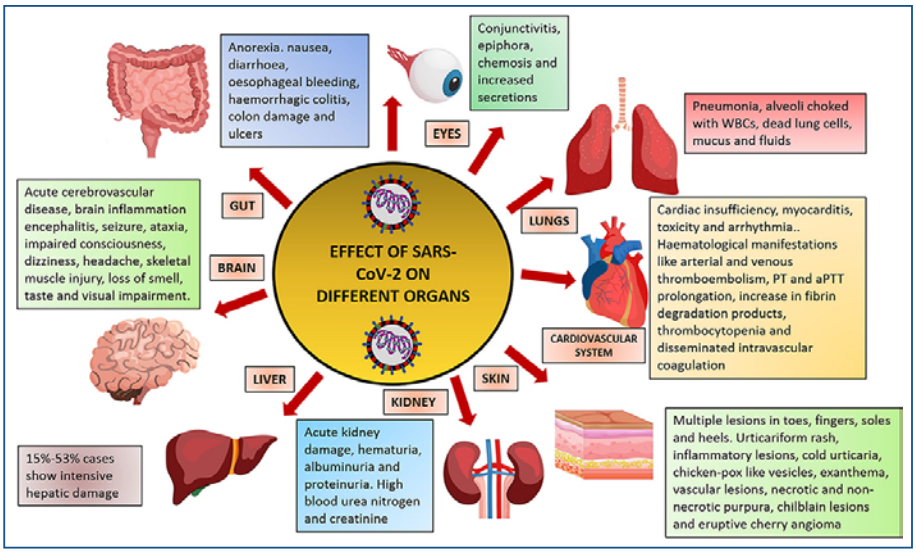
In view of the aggressive and invasive nature of the SARS-CoV-2 virus, which attacks multiple organ systems and causes a widespread inflammatory and pro-thrombotic state, it is not surprising that patients develop Long COVID (**Figure 2**). Furthermore, the lingering presence of the virus is associated with PASC. Endoscopic studies of small and large intestinal tissue in patients with inflammatory bowel disease (IBD) seven months after mild acute COVID-19 found SARS-CoV-2 RNA in 70% and viral nucleocapsid protein in 52% (but negative viral cultures). Patients with these viral antigens had multiple symptoms of Long COVID, including chest pain (3.1%), myalgias, palpitations, depression, dyspnea, coughing, diarrhea, sleep disorders, headaches, abdominal pain, anosmia, memory issues, and fatigue (56.3%). At least one symptom was present in 65.6% of patients who had persistent viral antigen – but none in the group with no viral antigen after the infection. The authors hypothesized that "viral antigen persistence instigates immune perturbation" and "serves as a basis for post-acute COVID-19."[4]

Figure 1. Long COVID conditions in a CDC study

- Respiratory symptoms
- Asthma
- Acute myocardial infarction
- Cardiac dysrhythmias
- Cardiovascular disease
- Heart failure
- Myocarditis
- Cardiomyopathy
- Neurologic conditions
- Cerebrovascular disease
- Gastrointestinal and esophageal conditions
- Smell and taste disturbances
- Renal failure
- Chronic kidney disease
- Pulmonary embolism
- Thromboembolic event
- Hemorrhagic conditions
- Mood disorders
- Other mental conditions
- Anxiety disorders
- Sleep disorders
- Malaise and fatigue
- Muscle disorders
- Musculoskeletal pain
- Diabetes (type 2 and type 1)

Test data show that 88.4 million Americans have been infected with COVID-19,[4] which means that about 18–20 million people (20–25%, based on CDC findings[2]) are affected by a variety of medical/surgical conditions included in PASC.[5] Amid diverse symptoms and multisystem damage, it is important to search for patterns and classifications. A prospective study found three distinct groups with Long COVID symptoms. Cluster 1 often had pain symptoms, including joint pain, myalgias, and headaches. Cluster 2 had mainly cardiovascular symptoms (chest pain, shortness of breath, palpitations). Cluster 3 was characterized by the lowest number of symptoms and the least disability, with fatigue and dyspnea as the most common conditions. There were fewer symptoms in Cluster 3 than Cluster 1 (2 vs. 6 per patient). As expected, the first two clusters showed greater functional and respiratory impairment, vocational disability, and lower scores of general health. The authors felt that classifying patients could reveal different pathophysiologic mechanisms and improve the assessment and treatment of Long COVID.[6] On the other hand, it is essential to be alert

Figure 2. Effect of SARS-CoV-2 infection on different organs of the human body



Source: Ashish Prasad and Manoj Prasad, Single Virus Targeting Multiple Organs: What We Know and Where We Are Heading? Front. Med., 05 August 2020, https://doi.org/10.3389/fmed.2020.00370, https://www.frontiersin.org/articles/10.3389/fmed.2020.00370/full

for unusual clusters of organ involvement, as in the following case report of a patient with cognitive, olfactory, cardiac, pulmonary, musculoskeletal, neuropathic, gynecologic, sleep, and psychological conditions that are part of her Long COVID syndrome.

CASE REPORT

A 51-year-old woman (with Moderna vaccination in April, May, and November 2021) tested positive for COVID-19 on January 1, 2022. Her symptoms included nasal congestion, laryngitis (with vocal loss for two days), dyspnea, tachycardia, chest pain, exhaustion, alternating warmth/chills, and severe weakness that made her arms feel extremely heavy. Her condition worsened due to tachycardia and orthostasis that caused two syncopal episodes. On January 10, 2022 her blood pressure was 90/60 (her baseline is 130/80). Her lab studies showed an elevated white cell count (13.1 k/uL); increased neutrophils (10.27, up to 8 is normal); C-reactive protein level of 6 mg/L (normal is less than 5); an elevated LDH (222 U/L, up to 214 is normal); and a D-dimer level of 3.72 ug/mL (less than 0.51 is normal). She was diagnosed with multiple symptoms related to COVID-19, including postural orthostatic tachycardia syndrome (POTS), for which she was placed on metoprolol (25 mg twice a day). She continued to feel severe fatigue, as if her body were weighed down with lead. To maintain her blood pressure, she was given compression stockings and advised to hydrate herself with a 50% solution of Gatorade and water (5 glasses a day minimum).

Additional evaluations during January and February 2022 included a stress test, Holter monitor, and a pulmonary function test. During an inconclusive stress test, she achieved only 60% of her predicted exercise capacity (a few minutes, up to 4.7 METs); her blood pressure rose from 100/60 to 112/62 and her pulse from 71 to 100 (with a blunted response due to metoprolol). The 48-hour Holter monitor showed primarily a sinus rhythm with a pulse ranging from 56–113; minimal atrial and ventricular ectopy; a few ventricular triplets; and no symptoms (while on metoprolol). Her pulmonary function test showed normal lung volumes, but with increased residual volumes and diffusion capacity, and a positive methacholine challenge that was "suggestive of reactive airways" (and likely related to COVID-19). She was started on a steroid inhaler (beclomethasone).

In a telemedicine evaluation on February 18, 2022 (Long COVID phase, six weeks after symptom onset), I learned that she was contending with neuropathic symptoms: "buzzing" in her hands and feet as well as a sensation of painfully tight gloves; her feet improved to some extent with compression socks. "Brain fog" affected her short-term memory and her ability to concentrate. Due to her cognitive impairment, on occasion she made errors like mailing the wrong document and missing an exit while driving – even with the use of her GPS. She had chronic fatigue and her activity level was generally impaired; some mornings she was unable to get out of bed, although she did have a few good days. Her cough had mostly resolved but left her with chest pain related to costochondritis. Her past medical history included back pain, irritable bowel syndrome, depression, dysmenorrhea and decreased endurance with exercise (but no diagnosis of asthma and no use of inhalers).

When I examined her in June 2022, she was using her steroid inhaler twice a day and occasional albuterol (since April) as a rescue dose – for reactive airway symptoms caused by COVID-19. After not menstruating for years while on Junel, she had irregular bleeding during March but it resolved after stopping her medication for a week. Compression stockings, hydration, and metoprolol (now 12.5 mg in the morning and 25 mg at night) had helped her chest pain and palpitations; she switched to taking her night dose two hours before going to sleep, to prevent supine tachycardia. She had insomnia before the viral infection, but Long COVID worsened her sleep pattern due to tachycardia (until metoprolol took effect) and neuropathic discomfort in her hands.

POTS and dehydration caused two episodes of passing out in one night; in one of these falls, a bracelet cut her wrist and her glasses caused an injury below an eye. She still had an uncomfortable "buzzing" sensation in her hands, but it was no longer constant. The post-COVID fatigue had decreased her activity level and therefore she had gained some weight. Some days, she felt "wiped out" and her arms felt "incredibly heavy." Recently, she rode her bicycle for 20 minutes for the first time since her infection and was extremely fatigued the next day. She had persistent cognitive impairment, especially with retrieving new material such as numbers or bits of information that she had just thought of, heard, or read. Despite these problems, she was able to work on a part-time basis (editing, consulting on policy matters, preparing reports).

Due to these persistent symptoms, she was referred to a rehabilitation program (3 times a week for 2–3 months) and a monthly Long COVID support group. A 6-minute walk test showed a baseline blood pressure of 112/64, 99% oxygen saturation, and a pulse of 78. At two minutes, her oxygen saturation declined to 93%. She walked at a rate of 2.3 miles per hour (2.8 METs); her fatigue level went from a baseline of 6 to 8; and she felt very tired as she had not slept well the previous night. Mental health surveys revealed that her level of depression was low; her anxiety was moderate; and her overall level of stress was high.

The examination revealed that she had no problems with her gait pattern and climbing steps. Vital signs while seated were pulse 68 and blood pressure 117/80, which changed to 80 and 107/75 (with no orthostatic symptoms) after standing. Her cranial nerves (2–12) were normal with visual acuity, extraocular movements, jaw and facial muscle function, facial sensation, hearing, palatal elevation, sternocleidomastoid and trapezius function, and tongue movements. Her olfactory sense was impaired; she misperceived the scent of cloves as cinnamon and could not smell vanilla and almond essences. Muscle strength was 5/5 at the shoulders, elbows, wrists, hands, hips, knees, and ankles; her tone was normal. The sensory examination revealed normal light touch, proprioception, and vibratory sense in all extremities. Reflexes were normal in the upper extremities, but decreased at the patellar and Achilles tendons. Her plantar responses were down-going. The cerebellar exam showed that she had normal finger-to-nose, rapid alternating movements, and heel-to-shin testing. She had a normal Romberg test. Range of motion at the shoulders, elbows, wrists, hands, hips, knees, and ankles was normal. Her lungs were clear to auscultation and her cardiac examination revealed a normal rhythm with no murmurs.

Cognitive testing with the Repeatable Battery for the Assessment of Neuropsychological Status showed that her score with learning a list of words was 30/40 and with recalling a short story was 15/24; copying a complex figure gave a score of 18/20; assessing the angles of intersecting lines was 17/20; naming fruits and vegetables in one minute was 18/40; recalling strings of digits was 11/16; matching symbols to numbers was 33/89; recalling the initial list was 7/10; and recalling the complex figure was 10/20. Her lowest score was in the domain of Attention (recalling strings of digits and matching symbols to numbers). Her highest scores were in the Immediate Memory and the Visual Spatial-Constructional domains, but were only at the 50th percentile for her age group. The composite score for all these subtests placed her in the 34th percentile of cognitive function. This result was clearly a decline from her baseline. She had graduated from Brown University, obtained an MSW degree, and then taught courses in writing and communication as an adjunct professor at two universities. At present, she works as an independent education consultant and freelance writer. She is diligent with her physical rehabilitation and has developed her own strategies for cognitive rehabilitation.

This case report is representative of patients with Long COVID, who can experience a variety of symptoms after disease onset. It also describes the diagnostic testing that many patients go through, often with minimal or no abnormal findings. Objective evidence that was consistent with Long COVID in this patient included elevated D-dimer, white blood cell, and C-reactive protein levels as well as orthostasis (POTS), a positive methacholine challenge, and a decline in oxygen saturation – more than four weeks after the acute infection. In many respects, Long COVID is a diagnosis of exclusion as patients and their providers search for explanations and treatable causes for their symptoms. Frequently, the symptoms outweigh the objective findings, and this can be frustrating and challenging for both patients and their physicians.

PUBLIC HEALTH ISSUES

It is vital that the healthcare system has clinicians who strive to understand, treat, and conduct research on the post-acute sequelae of COVID-19. At present, patients with Long COVID are eligible for rehabilitation along the entire spectrum of care. Depending on their clinical needs, which are associated with insurance criteria, patients can receive acute inpatient rehabilitation (3 hours/day of therapy); subacute rehabilitation (1–1.5 hours/day of therapy); home care (therapy 3 times a week); and outpatient rehabilitation (3 times a week). In the context of this public health crisis of disability, health care professionals and organizations should develop systems of care for the entire spectrum of Long COVID, with specialized clinics where clinicians can see large numbers of patients to improve their treatment for this complex syndrome and carry out essential research studies. Patients should also receive education about multisystem issues with Long COVID, including how to monitor themselves (e.g., self-oximetry), adapt, and improve their quality of life. Support groups through specialized clinics and online

communities, such as Survivor Corps, are also essential for long-term success in dealing with the myriad problems of Long COVID.[7]

Rhode Island and Brown University have been at the forefront of the pandemic, through the public health perspectives of Dr. Megan Ranney and Dr. Ashish Jha. We are also fortunate to have physicians like the authors in this special issue of the *Rhode Island Medical Journal*, who have contributed their invaluable clinical experience and knowledge of the latest medical literature on Long COVID. This issue includes articles on pulmonary, cardiac, neurological, cognitive, and orthopedic complications of Long COVID. As our knowledge of this syndrome evolves, we will need to address all the bodily systems that are vulnerable due to the ubiquitous presence of ACE2, which functions as a doorway for SARS-CoV-2. From the public health perspective, it is important to note that the US Department of Health and Human Services states that "Long COVID can be a disability under Titles II (state and local government) and III (public accommodations) of the Americans with Disabilities Act, Section 504 of the Rehabilitation Act of 1973, and Section 1557 of the Patient Protection and Affordable Care Act. Each of these federal laws protects people with disabilities from discrimination."[8] These legal protections and governmental support will be essential for clinicians, caregivers, and survivors with Long COVID.

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Disclosure

Dr. Mukand is working on a nonfiction narrative/self-help book about Long COVID and would like to interview people on the full spectrum of severity and conditions, especially visual, GI, hepatic, renal, skin, and musculoskeletal complications.

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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.

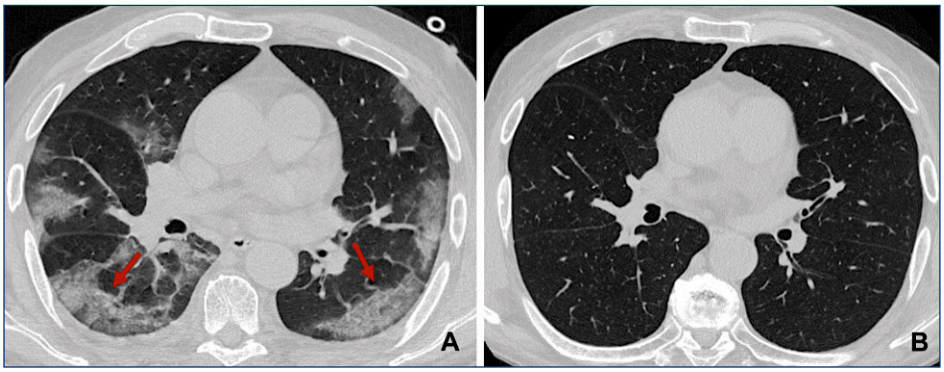
RESPIRATORY SEQUELAE

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]

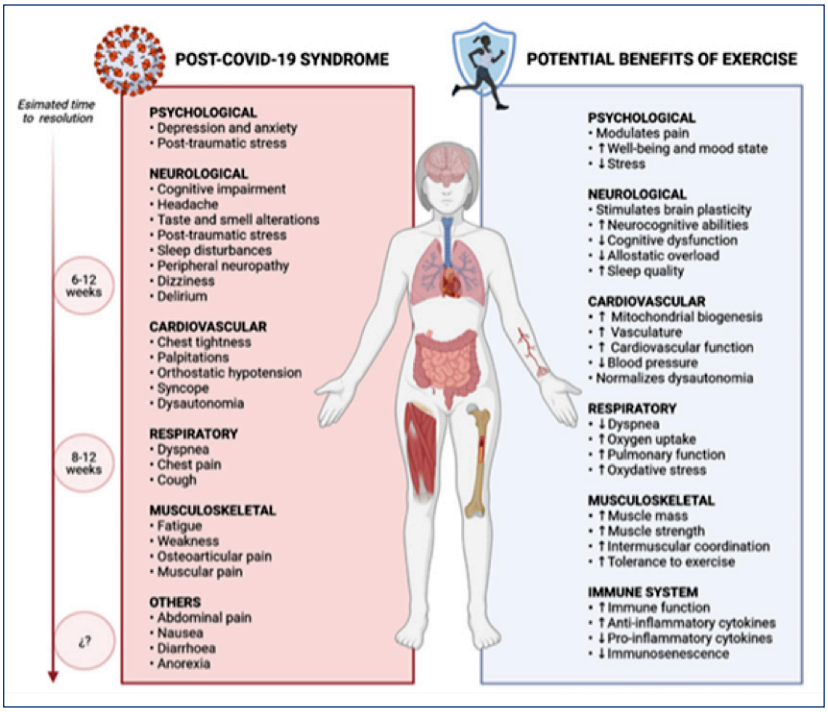
Supplemental oxygen should be prescribed to patients who have resting or exertional hypoxemia (generally oxygen saturation <88%) as in other chronic lung diseases; many patients do improve their DLCO, so the need for oxygen should be re-evaluated after two to three months. The diagnostic and therapeutic 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.

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Disclosure

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Long-term Cardiovascular Manifestations and Complications of COVID-19: Spectrum and Approach to Diagnosis and Management

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ABSTRACT

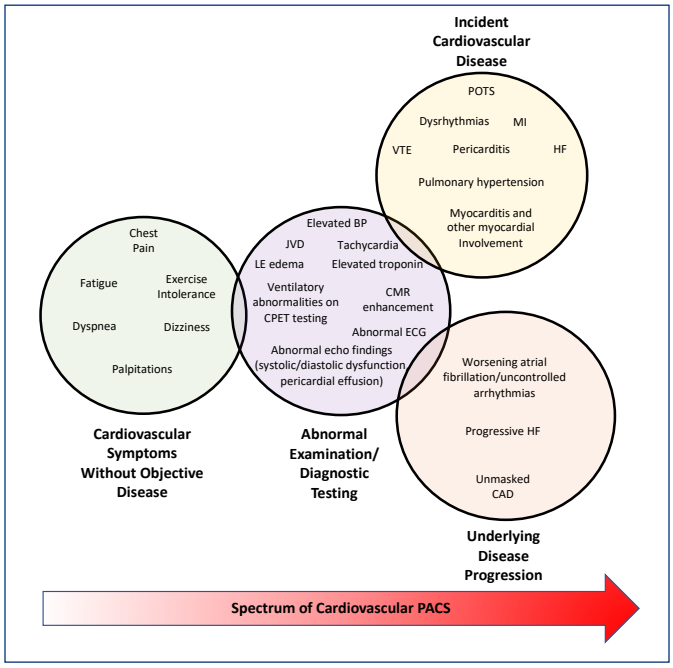
Survivors of coronavirus disease 2019 (COVID-19) may experience persistent symptoms, abnormal diagnostic test findings, incident disease in specific organ systems, or progression of existing disease. Post-acute COVID-19 syndrome (PACS) is defined by persistent, recurrent, or new symptoms, findings, or diagnoses beyond four weeks after the initial infection. PACS has been characterized as a multi-organ syndrome, often with cardiopulmonary symptoms that include fatigue, dyspnea, chest pain, and palpitations. Cardiovascular pathologies in PACS include new-onset arrhythmia, myocarditis, unmasked coronary artery disease, and diastolic dysfunction as well as abnormal findings on electrocardiogram, troponin testing, and cardiac magnetic resonance imaging. In this review, we discuss the cardiovascular symptoms, pathophysiology, clinical investigation, and management strategies for cardiopulmonary symptoms of PACS. We offer a treatment algorithm for primary care clinicians encountering patients with cardiopulmonary PACS and discuss ongoing research on this topic.

KEYWORDS: Post-acute COVID-19 syndrome; Long COVID; Post-Acute Sequelae of SARS-CoV-2; PASC; PACS; cardiovascular disease; CVD

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, or COVID-19) is characterized by both pulmonary and extrapulmonary manifestations, with acute cardiovascular effects including thromboembolic events, new-onset heart failure, myocardial infarction, and arrhythmias. There is growing recognition that some individuals may endure post-acute COVID-19 syndrome (PACS), defined by persistent, recurring, or new symptoms, signs, and/or diagnoses attributable to COVID-19 that extend beyond the acute phase (four weeks after onset of infection).[1] PACS, also known as post-acute sequelae of COVID-19 (PASC) or Long COVID, is a multi-organ syndrome that often has persistent cardiopulmonary symptoms including fatigue, dyspnea, chest pain, and palpitations.[2] PACS encompasses an array of new cardiovascular and other end-organ pathologies or progression/exacerbation of preexisting cardiopulmonary conditions.

Figure 1. Spectrum of cardiovascular symptoms, signs, and/or diagnoses observed in post-acute COVID-19 syndrome



BP–blood pressure; CAD–coronary artery disease; CMR–cardiac magnetic resonance imaging; CPET–cardiopulmonary exercise testing; ECG–electrocardiogram; HF–heart failure; JVD–jugular venous distention; LE–lower extremity; MI–myocardial infarction; PACS–post-acute COVID-19 syndrome; VTE–venous thromboembolism.

Cardiovascular pathologies in PACS may include new-onset arrhythmia, myocarditis, and diastolic dysfunction as well as abnormal findings on electrocardiogram (EKG), troponin testing, and cardiac magnetic resonance imaging (CMR) (in relation to specific clinical diagnosis or long-term clinical outcomes).[2-7] **Figure 1** provides an overview of PACS manifestations as it relates to the cardiovascular system. As more individuals, numbering in the millions, are infected by SARS-CoV-2 and survive the acute phase, it is of significant societal importance to understand the long-term sequelae of this disease.

In this review, we discuss the cardiovascular symptoms and pathophysiology of PACS, current clinical investigation and management strategies for cardiopulmonary symptoms of PACS, and ongoing investigations of cardiopulmonary PACS.

CARDIOVASCULAR SYMPTOMS OF PACS

Beyond the first 30 days of illness, COVID-19 survivors, both those who required hospitalization and those with milder cases, have reported a broad range of cardiovascular symptoms, including dyspnea,[8,9] chest pain,[8-10] palpitations,[8-12] dizziness and tachycardia[13] (**Table 1**[14,15]). Ramadan et al summarized the findings of 20 studies, with median time to assessment of 52 days post-COVID diagnosis, and noted dyspnea (median 33%; range 0–87%), chest pain (median 17.5%, range 0–73%), and palpitations (median 0.77; range 0–88%).[9] Prolonged symptoms were significantly associated with hospitalization for initial COVID-19.[12]

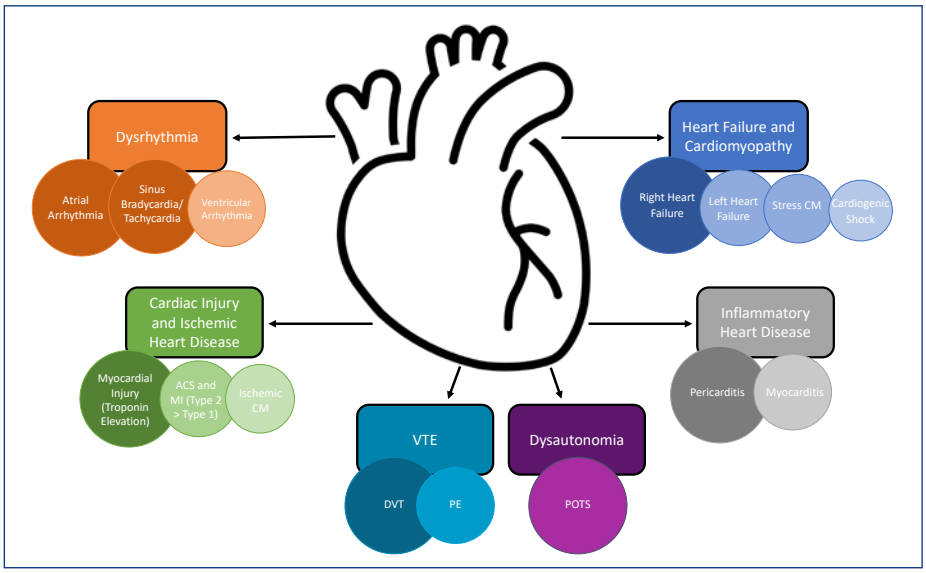
Table 1. Common cardiovascular symptoms and risk factors observed in patients experiencing post-acute COVID-19 syndrome.*

Symptoms	Risk Factors
Fatigue	Older Age
Dyspnea	Higher BMI
Chest Pain	Female Gender
Palpitations	Pre-COVID Cardiovascular Disease (CAD, HF, Arrhythmias)
Dizziness	Pre-COVID Comorbidities (DM, HTN, CKD, Chronic Lung Disease)
Tachycardia	Initial Symptomatic COVID-19 Illness
Exercise Intolerance	Limited Baseline Functional Status

*Table based on data reported by the American College of Cardiology and the American Heart Association task force and expert consensus groups.[14,15]

Figure 2. Cardiovascular complications seen in post-acute COVID-19 syndrome

Each diagnostic category is highlighted in different color. The specific diagnoses under each category are shown in circles. The size of the circle and the color scale represent the relative frequencies of each diagnosis, with larger areas and darker colors representative of higher relative frequency.



ACS–acute coronary syndrome; CM–cardiomyopathy; DVT–deep vein thrombosis; MI–myocardial infarction; PE–pulmonary embolism; POTS–postural orthostatic tachycardia syndrome; VTE–venous thromboembolism.

CARDIOVASCULAR PATHOLOGIES IN PACS

The various cardiovascular diseases that may be diagnosed in patients experiencing PACS, along with their relative frequencies highlighted with color coding, are shown in **Figure 2.**

PACS and arrhythmias

Arrhythmias have been identified both during the acute phase of infection and as part of PACS. Arrhythmia is one of the most common cardiac symptoms during acute COVID-19.[16] Coromillas et al found that the majority of patients with arrythmias during acute COVID-19 did not have a prior history of arrhythmia. Of those who did develop an arrhythmia, the majority (81.8%) had atrial arrhythmias, 20.7% had ventricular arrhythmias, and 22.6% had bradyarrhythmias.[16] However, Ingul et al performed 24-hour EKGs on patients 3–4 months after COVID-19 and detected arrythmias in 27% of patients, with PVCs as the most common arrythmia.[17] Musikantow et al retrospectively studied the incidence of atrial fibrillation and flutter in over 5,000 hospitalized patients with COVID-19 or influenza, and found similar rates in both groups, with an association between arrhythmia and elevations in inflammatory markers, myocardial injury, and death. The results suggest that atrial fibrillation and flutter during COVID-19 hospitalization may occur secondary to severe systemic disease.[18]

EKG changes including T-wave abnormalities, ST segment elevation and depression, right bundle branch block, and sinus tachycardia have been identified. These changes were mainly observed in studies assessing patients less than three months after diagnosis or recovery from the acute phase of COVID-19.[9] Xie et al analyzed 153,760 US Veterans diagnosed with COVID-19 who survived for 30 days and found an increased 1-year risk of dysrhythmias (including sinus tachycardia, sinus bradycardia, atrial and ventricular arrhythmias) compared to a large population-based control group (composite hazard ratio [HR] 1.69; 95% confidence interval [CI] 1.64–1.75).[19] A possible mechanism for post-COVID arrythmias is myocardial damage from the inflammatory cascade and subsequent fibrosis, remodeling, and arrhythmias.[20]

PACS and inflammatory heart disease

Myocardial and pericardial inflammation can be seen both in the acute phase of COVID-19 and in the post-acute phase. Xie et al found that beyond 30 days after infection with

SARS-CoV-2, individuals had a much higher relative risk of myocarditis (HR 5.38; 95% CI 3.80–7.59) and pericarditis (HR 1.85; 95% CI 1.61–2.13) compared to control cohorts.[19] Several studies have identified high rates of cardiac inflammation and pericardial enhancement on CMR up to six months post-hospitalization.[21,22] Cardiac findings on CMR include increased T1 and T2 intensity, late gadolinium enhancement, and pericardial effusion.[9] Although initial studies found high rates of abnormalities on CMR, particularly among athletes recovering from COVID-19,[23,24] few patients reported cardiovascular-related symptoms during follow-up.[25] Further, when evaluating autopsy results, only 1.2% met histological criteria for myocarditis.[26] CMR findings of myocarditis do not always seem to correlate with patient symptoms, calling into question its clinical significance.[26] Similarly, it appears that small pericardial effusions are relatively common in the post-acute period of COVID-19, but symptomatic pericarditis is rare.[13]

PACS, cardiac injury, and ischemic heart disease

Myocardial injury with elevated troponins, ischemia and infarction have been described in acute and post-acute COVID-19. Several mechanisms of myocardial injury in the setting of COVID-19 have been hypothesized, including a proinflammatory state from cytokine storm, direct viral invasion of myocytes, hypercoagulable state with thromboembolic phenomenon, coronary plaque instability, demand-supply mismatch with increased demand from systemic inflammation, and accelerated atherosclerosis and plaque rupture.[27-30] In the post-acute phase of COVID-19, the cytokine-mediated damage can cause thrombogenesis, decreased oxygen supply, coronary plaque destabilization, progression of chronic cardiovascular disease (CVD) into unstable disease, increased metabolic demand, and reduced cardiac reserve.[31] One study found that patients with COVID-19 had a three times higher likelihood of a major adverse cardiac event at a median of five months post-discharge compared to controls matched by age, sex, and risk factors .[32] The one-year incidence rates of ischemic heart disease, including acute coronary disease (HR 1.72; 95% CI 1.56–1.90), myocardial infarction (HR 1.63; 95% CI 1.51–1.75), and ischemic cardiomyopathy (HR 1.75 (95% CI 1.44–2.13) are all increased when compared to a control cohort without COVID-19.[19]

PACS, heart failure and cardiomyopathy

COVID-19 has been associated with several echocardiographic abnormalities. Right ventricular dysfunction,[33,34] likely secondary to pulmonary disease, was the most common finding. Other abnormalities include regional left ventricular (LV) systolic dysfunction, diastolic dysfunction, global hypokinesis, left ventricular hypertrophy, and pulmonary hypertension.[9,34] Xie et al found that patients with COVID-19 had a significantly higher one-year risk of incident heart failure (HR 1.72; 95% CI 1.65–1.80) than control patients.[19] Another study found an increased trend in Takatsubo cardiomyopathy both in the general population and in COVID-19 patients during the pandemic, thought to be secondary to isolation and stress as well as SARS-CoV-2 infection and illness.[35] Furthermore, patients with underlying heart failure are particularly vulnerable to disease exacerbation, progression, and decompensation in the post-acute period of COVID-19.[36,37]

PACS and dysautonomia

Cardiovascular autonomic dysfunction can be seen post-COVID, and it has been described as a postural orthostatic tachycardia syndrome (POTS)-like illness or orthostatic intolerance.[38,39] POTS has been suggested as a possible etiology for symptoms of chest pain, palpitations, and dizziness in patients with post-acute COVID-19 syndrome.

PACS and thromboembolism

Several studies have identified increased rates of thromboembolic events in both the acute and post-acute phases of COVID-19. In the post-acute phase, Xie et al found a significantly increased risk of deep vein thrombosis (HR 1.98; 95% CI 1.94–2.24), pulmonary embolism (HR= 2.93; 95% CI 2.73–3.15), and superficial vein thrombosis (HR=1.95, 95% CI 1.80–2.12) in patients who survived beyond 30 days after COVID-19 diagnosis.[19] A retrospective study that followed COVID-19 patients up to 30 days post discharge found that 2.5% had a thrombotic event including pulmonary embolism, intracardiac thrombus, and ischemic stroke.[40]

PACS, pulmonary hypertension, and right heart failure

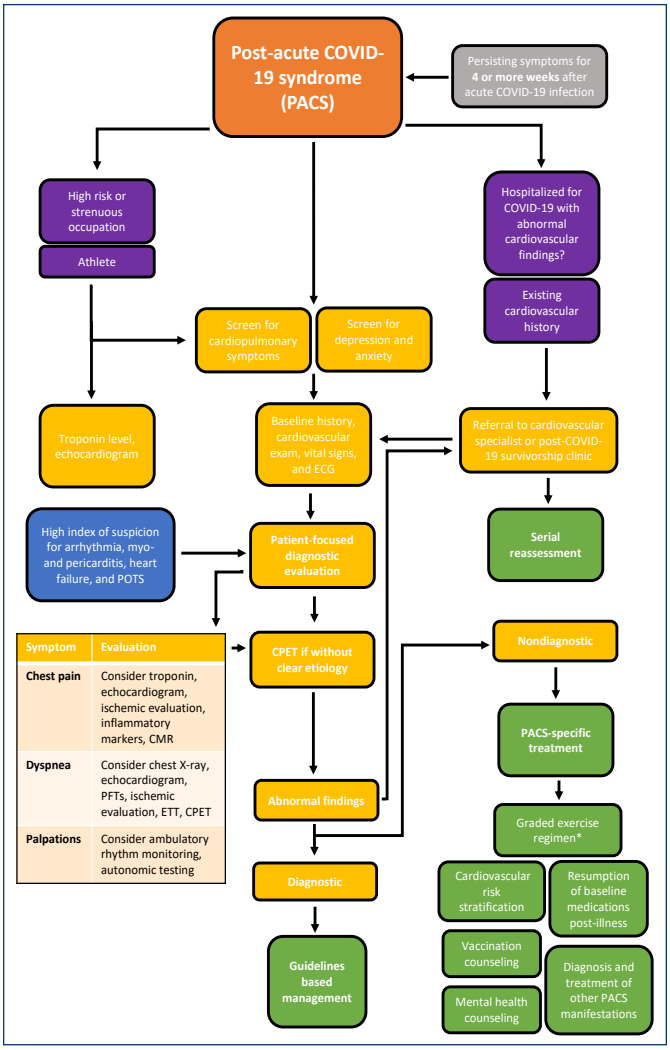
COVID-19 has been associated with pulmonary hypertension and right heart failure in those hospitalized during the acute phase of the disease.[41] Multiple mechanisms for developing pulmonary hypertension have been postulated, including inflammation, cytokine storm, endothelial injury, hypercoagulability causing venous thromboembolism, thrombotic microangiopathy, and vasoconstriction.[41] These pathophysiologic mechanisms are postulated to lead to either pre-capillary pulmonary hypertension or chronic thromboembolic pulmonary hypertension.[42] Additionally, pulmonary hypertension may be a result of hypoxia and significant lung injury from the acute disease. However, data on pulmonary hypertension and right heart failure as long-term manifestations of PACS are limited.

CURRENT CLINICAL MANAGEMENT STRATEGIES

As the number of COVID-19 survivors experiencing PACS continues to grow, clinical management strategies for the evaluation and treatment of cardiopulmonary symptoms are necessary. Ongoing treatment-focused clinical trials will ideally refine these strategies **(Table 1)**. Currently, however,

there is limited clinical guidance for clinicians to manage patients with cardiopulmonary symptoms attributed to PACS. Among professional societies, the European Society of Cardiology published a position paper in October 2021, offering strategies for outpatient cardiologists in the initial evaluation of PACS patients. Clinical management algorithms have also been published.[14,43-45] In May 2022, the American College of Cardiology Consensus Decision Pathway gave guidelines on cardiovascular sequelae of COVID-19 in adults, including myocardial involvement, cardiovascular manifestations of PACS, and return-to-play for professional and non-professional athletes.[44] In this review, we propose a clinical algorithm for patients with cardiopulmonary symptoms and signs after the acute phase of COVID-19 (**Figure 3**).

Figure 3. Clinical management algorithm for cardiopulmonary manifestations of post-acute COVID-19 syndrome



CPET–cardiopulmonary exercise testing; CMR–cardiac magnetic resonance imaging; ECG–electrocardiogram; ETT–exercise treadmill test; PACS–post-acute COVID-19 syndrome; POTS–postural orthostatic tachycardia syndrome.
*Graded exercise can be initially performed in semi-recumbent or recumbent positions (such as rowing and swimming exercise) for those with orthostatic intolerance.

The diagnosis of PACS can be made in a variety of healthcare settings. Among early studies of patient cohorts in multidisciplinary PACS clinics, clinicians found that some cardiopulmonary symptoms and complications after COVID-19 were not always proportional to the severity of the acute disease.[46] However, disease severity in general has emerged as a predictor of PACS cardiopulmonary symptoms and complications.[19,47] Referrals to cardiovascular or PACS clinics are not necessarily dependent on the severity of the acute disease. Referral is especially important for patients with cardiovascular comorbidities and manifestations of PACS, given their increased risk of morbidity and mortality.[7,48]

Due to the cardiovascular burden of COVID-19, current guidance tailors the clinical history, vital signs, and physical examination to search for new arrhythmias, POTS, myo- and pericarditis, heart failure, and unmasked coronary artery disease.[44,45,49] Universal cardiovascular testing strategies have also been considered; among athletes with persistent cardiopulmonary symptoms attributed to PACS, the American College of Cardiology guidelines for determining return-to-play recommended "triad testing" with EKG, high-sensitivity troponin, and echocardiography.[14]

Balancing the investigation of cardiopulmonary symptoms after acute COVID-19 against the potential risks of false-positive findings and overdiagnosis, we agree with symptoms-based diagnostic evaluation that adheres to professional guidelines.[44,45,50] The range of testing for cardiopulmonary PACS is broad, and includes imaging, cardiac biomarkers, and even cardiac catheterization. Cardiopulmonary symptoms, particularly in PACS, pose a diagnostic challenge in determining if they are primarily attributable to cardiovascular or pulmonary pathology.[45] Careful diagnostic testing that addresses positive and negative findings of both cardiovascular and pulmonary disease, such as echocardiography and chest computed tomography, will assist clinicians in evaluating patients with PACS. In patients with unexplained persistent cardiopulmonary symptoms, cardiopulmonary exercise testing (CPET) may identify objective abnormalities and classify them as cardiac, vascular, pulmonary, muscular, or some combination of multisystem involvement; this will allow a more directed approach to treatment.[51]

The management of cardiopulmonary diseases linked to PACS, including acute coronary syndrome, pulmonary embolism, and myocarditis, has largely been informed by established professional guidelines. Treatment recommendations for persistent symptoms, in the current investigational landscape, are primarily supportive.[44,45] Multiple treatment algorithms suggest cardiopulmonary rehabilitation, if without contraindication, as well as mental health counseling.[43–45,52] Another algorithm noted the potential overlap between cardiopulmonary symptoms of PACS and deconditioning attributable to acute COVID-19, with a

recommendation for graduated exercise regimens, including recumbent or semi-recumbent exercises (e.g., swimming) for those with significant postural symptoms. Other standard pharmacological and nonpharmacological approaches (e.g., compression stockings, midodrine, beta-blockers) may help patients with autonomic dysregulation (e.g., orthostatic hypotension, inappropriate sinus tachycardia, POTS, palpitations).[14] Clinicians may also consider screening PACS patients with questionnaires for depression and anxiety, such as the Patient Health Questionnaire-9 and the General Anxiety Disorder-7; both conditions have been associated with PACS, may exacerbate symptoms, and are linked to cardiovascular disease.[11,53] All clinicians caring for PACS patients with persisting cardiopulmonary symptoms should recommend COVID-19 vaccination if without contraindications, given the association of vaccination with improvement in PACS symptoms demonstrated in prior studies.[54]

ONGOING TRIALS AND FUTURE DIRECTIONS

Moving forward, research priorities for cardiopulmonary problems of PACS should include: clarifying the pathophysiology of PACS; identifying patient populations that are vulnerable to cardiopulmonary PACS (as well as specific risk factors); and developing treatment modalities for PACS. Numerous trials are currently investigating cardiovascular outcomes in patients with PACS. Treatment trials for cardiopulmonary PACS have focused on the effects of cardiac and pulmonary rehabilitation, though metoprolol succinate for PACS symptoms is also under investigation.[55] Additionally, since the start of the COVID-19 pandemic, researchers globally have recruited large cohorts of individuals with a history of COVID-19 for further investigations into cardiovascular outcomes associated with PACS.[45] Multidisciplinary PACS clinics are foundational to research efforts, serving as referral centers to benefit patients as well as to recruit longitudinal cohorts for the epidemiologic study of PACS. Such efforts should be supported by public and private funding for advancing clinical understanding and treatment strategies, including pharmacologic management, for cardiopulmonary disease associated with PACS.

Despite strong public interest and its significance to population health, PACS research will continue to face substantial challenges. The nature of PACS as a disease, characterized by persisting symptoms frequently without a readily identifiable pathophysiology, may prove difficult to measure and diagnose.[56] For measurement, the utilization of remote patient monitoring data may offer new opportunities for PACS research, such as in investigations of arrhythmia or cardiopulmonary symptom burden.[43] The clinical course of cardiopulmonary PACS may ultimately differ by variants implicated in the initial infection. More broadly, observational studies for PACS research would benefit from uniform eligibility criteria, with comparator groups that have negative SARS-CoV-2 testing, and geographic and temporal comparability. Specifying uniform entry criteria between cases and controls will help ensure that these studies are able to elucidate the causal nature of long-term CVD complications arising in survivors of acute COVID-19.[57]

CONCLUSION

PACS, defined by the persistence or recurrence of symptoms or diagnoses attributable to COVID-19 beyond four weeks after initial infection, is increasingly recognized among COVID-19 survivors. Cardiopulmonary manifestations include persistent dysrhythmias, inflammatory disease, ischemic disease, heart failure, and dysautonomia. Current clinical management strategies for cardiopulmonary PACS emphasize diagnostic pursuit of symptoms based on clinical history, vital signs, and physical exam, as well as focused diagnostic testing starting with EKG. Athletes and those in high-risk or strenuous occupations may benefit from troponin testing and echocardiogram in their initial evaluation. Treatment for symptoms of cardiopulmonary PACS largely involves graded exercise and supportive measures, while new or worsening cardiovascular disease should be treated in accordance with best-practice guidelines. Numerous trials for cardiopulmonary PACS treatment are ongoing, primarily focused on the role of cardiopulmonary rehabilitation.

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Acknowledgment

Vishal Khetpal, MD, and Julia Berkowitz, MD, are co-first authors of this manuscript.

Funding Sources

The research reported/outlined here was supported by the Department of Veterans Affairs, Veterans Health Administration, VISN 1 Career Development Award to SE. SE is also funded by Center for Aids Research, The Rhode Island Foundation, and Lifespan Cardiovascular Institute. JLR, WW, and SE are funded by the VA Health Services Research and Development Center of Innovation in Long Term Services and Supports (CIN 13-419; C19-20-213). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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Neurological Sequelae of COVID-19 in Rehabilitation Settings

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ABSTRACT

Neurological symptoms of post-acute sequelae of COVID-19 (PASC), also known as Long COVID, are recognized. Four neurological syndromes (transverse myelitis, ischemic stroke, headache, and Guillain-Barré syndrome) associated with PASC are reviewed here, with a particular focus on issues related to rehabilitation.

KEYWORDS: Long COVID, neurological, rehabilitation

INTRODUCTION

The World Health Organization (WHO) defines Long COVID as symptoms lasting at least two months after a probable or confirmed diagnosis of COVID-19, usually starting within three months of COVID-19 onset.[1] This syndrome is also described as post-acute sequelae of COVID-19 (PASC). Neurological symptoms of PASC are variable and include fatigue, cognitive impairment, headache, myalgia, sensorimotor abnormalities, seizures, and dysautonomia.[1,2] Several neurological syndromes have been described in relation to PASC. In the absence of specific evidence for these syndromes, their treatment typically proceeds according to that for similar but non-COVID-related entities. For example, COVID-19-associated Guillain-Barré Syndrome (GBS) is treated in the same way as pre-pandemic GBS. Due to the prolonged symptoms in some COVID-19 cases, rehabilitation strategies are increasingly used to improve outcomes and hasten recovery.

In this review, we focus on four COVID-19-associated neurological syndromes that may benefit from inpatient or outpatient rehabilitation. These include GBS, transverse myelitis (TM), ischemic stroke, and headache. We will discuss the typical clinical presentation, theorized pathophysiology of these syndromes, and potential rehabilitation needs and treatments.

TRANSVERSE MYELITIS

Transverse myelitis (TM) is focal inflammation of the spinal cord, resulting in neurologic deficits (weakness, sensory loss, bowel/bladder dysfunction). Common causes include multiple sclerosis, neuromyelitis optical spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein associated disease (MOGAD), and neurosarcoidosis. A handful of cases of TM have been reported in the context of PASC,[3-8] and there are two theorized mechanisms for this condition. The first postulates viral invasion of the CNS via the ACE2 receptors on the brain/spinal glial cells and the endothelial cells of the blood brain barrier. The second proposed mechanism is a post-infectious autoimmune mediated response.[3]

TM presents clinically with acute to subacute focal neurologic deficits that correlate to the area of spinal cord inflammation. COVID-19-associated TM has been seen in both the acute phase of the illness as well as up to one month after the acute COVID-19 phase.[4,7] This time frame would support the proposed pathophysiology of direct viral invasion and post-inflammatory autoimmune response, respectively.

On MRI scans, both longitudinally extensive spinal cord lesions and multifocal cord lesions have been described in COVID-19-related TM. The cervical and thoracic segments of the spinal cord are most often implicated, and within the cord the ventral horns are most commonly affected. The ventral horn predominance correlates with patients typically presenting with primarily motor symptoms. Notably, this ventral horn predominance is also seen in other viruses that infect the spinal cord directly (e.g., polio, flaviviruses, and enterovirus).[3] The standard treatment of TM, including that associated with COVID-19, consists of high-dose steroids and frequently the addition of either plasmapheresis or intravenous immunoglobulin (IVIG). Patients with COVID-19-associated TM had various degrees of clinical improvement. One report showed complete recovery after a course of steroids and IVIG,[5] but most cases with COVID-19 TM do not fully recover over the first several days and require physical rehabilitation.

Given the small number of case reports describing TM with PASC, there are limited data regarding specific rehabilitation outcomes. In non-COVID TM, long-term follow up shows that approximately one-third of patients recover with minimal to no impairment; one-third have moderate disability (e.g., independent ambulation with mild spasticity, some manageable urinary/bowel changes, sensory deficits); and one-third have severe disability (e.g., inability to walk independently, no sphincter control).[9] The aim of physical rehabilitation in these patients is to maximize their independence and capabilities. Physical and occupational therapists focus on strength and range-of-motion to improve

tone, mitigate pain, and maximize functional mobility and independence with daily activities. Generally, in spinal cord injury rehabilitation, individuals with an injury at or below T12 may regain independent ambulation with assistive devices. Patients with cervical and high-thoracic lesions do not have as good a prognosis for ambulation. TM associated with COVID-19 is typically of the cervical and thoracic segments, but the outcomes data for this cohort are insufficient to make any generalizations about the prognosis for ambulation. Regardless, it is important to begin rehabilitation early and aggressively as about a third of patients with TM have a chance of near complete recovery.[10] Furthermore, the recovery process for TM can go on for a year or more, so it is important to periodically re-evaluate patients for additional courses of physical and occupational therapy. Overall, it appears that Long COVID-associated TM patients who are treated early on with high-dose steroids and IVIG in conjunction with a physical rehabilitation program will have the best prognosis and a chance for full recovery.

ISCHEMIC STROKE

Ischemic strokes have been associated with COVID-19. A systematic review during the first six months of the pandemic showed that the average incidence of ischemic stroke in COVID-19 patients was 1.5%[11] and a retrospective cohort study (March to April 2020) showed a 0.9% incidence of stroke, with a disproportionate number having strokes of uncertain etiology (cryptogenic).[12]

The theorized mechanisms of COVID-19-associated ischemic stroke are cardiomyopathy and/or hypercoagulability.[11,13] This hypercoagulability includes elevated D-dimer and fibrinogen levels or fibrin/fibrinogen degradation products as well as elevated pro-inflammatory cytokine levels and direct damage to endothelial cells.[11,13] In an early study, patients with COVID-19 had a much higher incidence of cryptogenic strokes as compared to non-COVID-19 patients.[12]

Depending on the location of the cerebral infarct, ischemic stroke can present with a variety of symptoms. Rehabilitation must be tailored to a patient's unique needs by an interdisciplinary team. Rehabilitation treatments after non-COVID stroke focus on improving mobility and activities of daily living (ADLs), often by helping patients practice and relearn basic activities.[14,15] The rehabilitation team will also address bowel and bladder function, pain management, psychological issues, and education of the patient and family. Most clinical recovery takes place in the first 3–6 months after stroke.[14]

There are no data about rehabilitation in patients with stroke related to COVID-19. An important consideration in discussing rehabilitation approaches is that patients with stroke in the context of COVID-19 had more severe strokes at admission and worse functional outcomes than those without the viral infection.[16] Therefore, they are likely to require more intensive and longer periods of inpatient rehabilitation.

HEADACHE

Headache is one of the most common neurological symptoms of COVID-19.[17,18] In patients with acute COVID-19, 11–34% reported a headache, and 5–55% of patients experienced headaches three months after the acute infection.[19] There is no known pathophysiology for these headaches, but a plausible mechanism is the release of cytokines and chemokines by macrophages during infection.[20] It is also theorized that the SARS-CoV-2 virus may activate trigeminal nerve endings, directly or indirectly, via vasculopathy and/or circulating cytokines/chemokines.[21]

The headaches described in COVID-19 are usually bitemporal, pressure-like or pulsatile, and may have associated migrainous photophobia/phonophobia.[19,21,22] They usually occur on a daily basis and are more prevalent in patients with underlying medical comorbidities (hypertension, coronary artery disease, diabetes, and hypothyroidism).[17] They are also difficult to control with standard treatments for tension or migraine headaches.

In some instances, COVID-19-associated headaches are refractory to standard management, and there is increasing interest in an interdisciplinary approach, similar to post-concussion headache management. There is wide variation in the structure of concussion clinics, but most have some combination of specialists in neurology, physical medicine and rehabilitation, sports medicine, social work, physical therapy, occupational therapy, and psychology.[23] In interdisciplinary concussion clinics, these clinicians work together to treat the complex causes of post-concussive headaches. The Mayo Clinic has been introducing Long COVID patients with headaches to their Brain Rehabilitation clinic that previously was reserved for concussion patients. Using the concussion clinic as a model, the interdisciplinary management of Long COVID headaches may be the best option for rehabilitation of these patients.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré Syndrome (GBS) is an autoimmune peripheral polyneuropathy characterized by ascending weakness and/or sensory loss.[24] Pre-pandemic GBS was frequently a post-infectious illness associated with campylobacter jejuni as well as Epstein Barr virus, mycoplasma pneumonia, Haemophilus influenzae and influenza A. It is thought to be caused by molecular mimicry, the theory in which foreign antigens have structural similarities to self-antigens and thereby trigger an autoimmune reaction.[24]

GBS associated with COVID-19 is considered primarily a post-infectious syndrome, but some studies have also shown

a para-infectious variant.[25-27] Molecular mimicry is the postulated pathological mechanism of GBS, and a study by Lucchese and Floel showed this mimicry between COVID-19 and human heat shock proteins.[28] The mechanism in the less frequent, para-infectious variant of COVID-19-associated GBS is thought to be caused by direct injury to nerves and/or an underlying immunodeficiency.[29]

As in conventional patients with GBS, those with COVID-19 are most often treated with IVIG or plasmapheresis. Follow-up and outcome data on patients with COVID-19 are limited, but a review noted that in an unspecified "short" time interval, 62% of patients with GBS had significantly improved or recovered.[25] Radisic et al showed that there was no difference in disability score between GBS patients with or without COVID-19 at three months after hospital discharge.[31] In a study of eight patients, Solaro et al showed that COVID-19-associated GBS had better outcomes than non-COVID-19 GBS.[32]

There are limited data on rehabilitation methods and outcomes for patients with COVID-19-associated GBS, but most case reports suggest an interdisciplinary approach with physical, occupational and speech/swallow therapy. Rehabilitation in these cases has mainly focused on functional training for safety and independence through exercises for strength, balance, and range-of-motion.[30,33]

Data on the rehabilitation of non-COVID-related GBS may be helpful. A study by Prada et al showed that continuing physical therapy for more than six months can improve functional outcomes in GBS.[34] A randomized controlled trial by Khan et al showed that at 12 months, patients with high intensity rehabilitation (three 1-hour sessions per week with PT, OT, psychology and speech therapy) scored better on scales of functional status and their perception of the disease.[35]

CONCLUSION

COVID-19 can be associated with long-lasting neurologic symptoms. In this article we discussed four neurologic syndromes associated with COVID-19 that may benefit from interdisciplinary rehabilitation strategies. There is limited data on outcomes of rehabilitation in these COVID-19-associated conditions, but using the non-COVID neurological syndromes as models is the first step toward more effective treatment of these patients.

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Acknowledgments

Dr. Stiles and Dr. Weisbach contributed equally to the preparation of this manuscript as co-first authors.

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Cognitive Complications of COVID-19 Infection

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ABSTRACT

SARS-CoV-2 is associated with a post-infectious neurocognitive syndrome characterized by fatigue and deficits in attention, memory, and executive function. As screening cognitive testing generally remains normal, the pathophysiologic basis of these symptoms remains controversial and there is no standardized treatment paradigm. We present a clinical case demonstrative of typical neurocognitive sequelae of SARS-CoV-2 infection, highlighting medical and social factors that may have contributed to the severity of symptoms. We discuss the pathophysiologic evidence for cognitive "brain fog" following COVID-19 infection as well as lifestyle changes and rehabilitation strategies that may improve recovery. As the benefits of pharmacologic therapy remain unproven, we close with a brief discussion of medication options that might be appropriate targets for future clinical trials in the context of rehabilitative treatment.

KEYWORDS: Long COVID; PASC; brain fog; dysexecutive syndrome

CLINICAL CASE PRESENTATION

A 56-year-old woman with no significant medical history was infected by SARS-CoV-2 in October 2020, prior to the availability of commercial vaccinations. She experienced mild respiratory symptoms with loss of her sense of taste and smell, and then developed fatigue, difficulty concentrating, severe dyspnea on exertion, and exertional tachycardia. When these symptoms persisted for five months, she sought multidisciplinary care from infectious diseases, neurology, and cardiology specialists.

She had remained out of work because fatigue and cognitive symptoms limited her abilities and she was unable to meet the requirements of her demanding clerical job. She felt a general fogginess of mind, accompanied by forgetting details, trouble concentrating, and a remarkable difficulty with multitasking, which was well below her baseline. She also slept for long periods during the day but had difficulty remaining asleep at night and overall had poor sleep quality. She was unable to return to her regular exercise regimen due to her fatigue and exertional symptoms.

Her initial neurological evaluation revealed a perfect score (30/30) on the Mini-Mental Status Examination, a normal neurological examination without neglect or focal cognitive symptoms, and a normal electroencephalogram and magnetic resonance image (MRI) of the brain. She was treated conservatively, with recommendations to engage in intellectually stimulating activities and practice sustaining attention to specific tasks (in her case, meditation and yoga).

She attempted a gradual return to work, but failed to perform as required. During a particularly alarming episode, she could not recall the details of a conversation on the previous day, even with cueing. Due to her residual cognitive impairments six months following infection, she was referred for a formal neuropsychological evaluation.

In contrast to her normal performance on cognitive screening tests, her deficits on a neuropsychological test battery were striking. She had mild to moderate impairments in multiple domains, including attention, processing speed, executive control, fine motor dexterity, learning, and memory. However, these deficits were present only in a subset of tests of executive control within each cognitive domain. Notably, embedded measures of mood and effort showed no evidence of depression or intentional underperformance. She was diagnosed with a dysexecutive pattern of cognitive impairment and met criteria for mild neurocognitive disorder.

A trial of donepezil subjectively improved the cognitive symptoms, but without clear objective benefit. Her cardiac evaluation showed evidence of myocarditis and she underwent cardiac rehabilitation with a gradual return to her previous exercise tolerance and frequency. Ten months after her infection, she returned to work part-time but was able to perform at only 20% of her previous productivity level. She continued to work on sustaining attention to single tasks and avoided multitasking in order to complete her work duties.

Repeat neuropsychological testing a year later demonstrated improvements in executive aspects of attention and cognitive flexibility, but her memory and semantic fluency were unchanged. Seventeen months following her initial infection, she continued to meet neuropsychological criteria for mild neurocognitive disorder. She did not regain her sense of smell or taste. Her overall cognitive profile was consistent with the emerging literature on the Long COVID neurocognitive syndrome.

COGNITIVE SYMPTOMS FOLLOWING SARS-COV-2 INFECTION

The post-acute sequelae of SARS-CoV-2 infection (PASC) are a growing health crisis, estimated to currently impact 110,000 Rhode Island residents.[1] PASC is an umbrella term for multisystem involvement (pulmonary, cardiac, musculoskeletal, etc.) that persists longer than 4 weeks after the acute COVID-19 infection. This article focuses specifically on the cognitive PASC that cannot be readily explained by acute events during infection, such as global hypoxic injury or stroke.

Our patient provides a typical example of the neurocognitive syndrome associated with SARS-CoV-2 infection, and case series have consistently highlighted a range of deficits in executive function.[2,3] Here, executive function refers to the cognitive processes (e.g., organization and planning) that control our more basic cognitive functions.[4] Executive control is less important for routine or memorized behaviors but is critical when we are confronted with novel tasks, unfamiliar environments, or conflicting rules. These situations arise routinely in day-to-day human life.

Given the major influence of executive function over other cognitive domains, it follows that dysexecutive impairments can cause difficulties in attention, concentration, processing of new information, task selection and monitoring, and manipulation of working memory.[4] Multi-tasking is especially impaired, because the difficulty of each simultaneously performed task is effectively multiplied.[5]

Executive dysfunction is experienced uniquely by each patient. Some may present with a specific concern such as forgetfulness or trouble focusing and others with subtle global dysfunction that causes them to feel foggy or slow. The primary symptom is likely related to the cognitive domain that is most stressed in the patient's life. Function outside the home is likely to be more impaired than at home, where habits and routines can compensate.

Regarding the incidence of cognitive PASC, high quality prospective data are limited because many large studies only asked about fatigue, did not control for acute stroke or hypoxia, or had study design biases. Acknowledging these challenges, current estimates range from 7% to 54%,[6] with individual cohort rates as high as 81%.[7,8]

There are some studies of cohorts similar to our patient. A longitudinal prospective study[9] followed subjects who had premorbid cognitive, MRI, and EEG data, and excluded patients who were hospitalized, required oxygen, or developed new MRI lesions. Patients who became SARS-CoV-2 seropositive averaged a 2-point decline in their Montreal Cognitive Assessment (MOCA, maximum score 30) from baseline, and 21% experienced a loss of 4+ points, which met the criterion for measurable cognitive decline in this cohort.

Critically ill patients have higher rates of cognitive dysfunction following COVID-19, but this is proportional to their higher rates of stroke and other medical complications.[10] Some propose that critically ill patients may suffer from a concurrent post-ICU syndrome that is not unique to COVID-19,[11] creating a multifactorial cognitive disorder with complicated rehabilitation needs.

Unfortunately, the benefit of vaccination in preventing PASC is limited. In one review of VA medical records, vaccination was associated with only a 15% relative risk reduction of developing PASC following breakthrough infection, though sub-analysis verified protective benefit specifically against cognitive dysfunction.[10] Thus, even with widespread vaccination, a significant clinical population will experience cognitive changes following COVID-19 infection.

It remains to be seen whether emerging COVID-19 variants will be associated with similar rates of cognitive dysfunction. In population-level studies, the Omicron variant had half the incidence of PASC compared to the Delta variant,[12] but available studies do not distinguish cases on the basis of variant. Similarly, the link between neurological and other systemic manifestations of PASC is not well studied.

PATHOPHYSIOLOGY OF COGNITIVE SYMPTOMS

Even mild SARS-CoV-2 infection is associated with up to a 20% risk of developing dysexecutive cognitive impairment.[2,9] This is seen across multiple case series with varying disease severity,[13,14] cognitive assessment tools,[8] various cultural settings,[8,9,15,16] and age groups including the asymptomatic elderly.[17] We argue that it represents a distinct clinical entity with a physiologic basis that is under investigation.

There are ongoing efforts to explain how SARS-CoV-2 infection results in prolonged cognitive dysfunction. An inflammatory process is suspected,[18] whether from direct viral activity in the brain[19,20] or through a parainfectious process. The inflammation may be more prominent in limbic and frontomedial regions of the brain, as they are closer to the olfactory epithelium.[21–23] The pathophysiologic process involves endothelial disruption,[24] microglial activation,[19] neurotransmitter depletion,[25] and microvascular compromise.[26] This process appears to cause leukoencephalopathy[27] and accelerated focal and global cortical atrophy,[21] with resultant network dysfunction and cognitive changes.

No studies provide strong evidence for using anti-viral or anti-inflammatory medications to prevent or treat cognitive PASC. As the NIH COVID-19 Treatment Guidelines Panel does not recommend steroid therapy for patients that do not require oxygen support,[28] any retrospective study would likely be confounded by differences in disease severity or degree of hypoxia. This remains an avenue for further clinical investigation.

CLINICAL MANAGEMENT OF COGNITIVE PASC

As there is no established treatment regimen, the management of cognitive symptoms following SARS-CoV-2

infection focuses on supportive care and the identification and treatment of other confounding medical factors. A high index of suspicion is necessary to recognize the dysexecutive pattern typical for neurocognitive PASC. This syndrome may present as a specific cognitive concern, as generalized fogginess or trouble with concentration or memory, or as difficulty at work or in community activities. Generally, elderly people and those with premorbid intellectual or cognitive disability are disproportionately affected.

Inappropriate behavior or violations of social norms should raise concern for alternative frontal lobe pathology. Similarly, a patient showing progressive declines over time should raise concern for an underlying degenerative process versus another comorbid risk factor for cognitive impairment. It is also possible that cognitive PASC could be superimposed on premorbid neurological conditions.

Patients should undergo a thorough screening for alternative causes of cognitive dysfunction, including a basic metabolic panel, complete blood count, vitamin B-12 and folic acid levels, thyroid function tests, a routine non-contrasted MRI of the brain, and other tests guided by the clinical picture. A relatively normal brain MRI is expected and structural lesions should prompt pursuit of alternative diagnoses such as ischemic stroke or frontal lobe tumor. If leukoaraiosis or ischemic white matter disease is detected, then aggressive control of microvascular risk factors should be initiated, with screening for hypertension, diabetes, and hyperlipidemia. Any comorbid mood or sleep disorders (e.g., depression or sleep apnea) that may contribute to poor cognitive performance should also be addressed.

If the initial diagnostic workup is reassuring, we recommend a period of symptom monitoring with a patient-directed cognitive rehabilitation regimen. Lifestyle changes for improved brain health include intellectually stimulating activities, community engagement, good sleep quality, smoking cessation, avoidance of mind-altering substances such as marijuana and alcohol, regular exercise, and a healthy diet.

A core challenge in the dysexecutive syndrome is that difficulties with attention and working memory often leads to a marked loss of the ability to multitask. To compensate for this, we recommend activities that allow focusing on a single task or thought process for progressively longer periods of time. In this manner, one can complete a series of tasks efficiently, allowing progression through a list and achieving a level of productivity that is similar to multitasking. In our case, yoga and meditation were recommended; however, one may find similar benefits in other exercises or outdoor activities, a game or puzzle, an art or crafting activity, reading a book, or enjoying music. In contrast, television or video media can impair sustained attention due to frequent scene changes and distracting elements.[29] This approach is similar to the strategies for improving executive functioning following traumatic brain injury.

There have been mixed reports regarding the potential for COVID-19 vaccination after acute infection to improve PASC symptoms.[30] Vaccination appears to be safe and does not worsen symptoms or quality of life.[31] Given the possibility of reinfection (and further cognitive insults) and the modest but measurable protection that vaccination offers, we recommend full vaccination with booster doses following CDC guidelines if the patient has not undergone it.

Regarding medical management of PASC, there are no available clinical trials to support the use of any particular pharmacotherapy. In the acute phase, selected sigma-1 receptor modulating antidepressants (e.g., fluvoxamine) have been postulated to have a neuroprotective role,[32] but this has not translated into a treatment recommendation for acute or post-acute care. Case reports, such as in this article, do not demonstrate clear and consistent benefits, and the side effects of cognitive stimulants can be significant.

Further pharmacologic insights might be gleaned from a related condition that is often compared to the post-COVID brain fog, that of chemotherapy-induced cognitive impairment. The effects of various classes of cognitive enhancers have been reviewed in this context.[33] In general, results were promising in small and carefully selected patient cohorts, often with preexisting cognitive difficulties. Clinical trials are ongoing, and no general treatment recommendation can be made at this time.

Given the lack of high-quality clinical data and the concern for side effects and adverse cognitive changes, we do not recommend routine pharmacotherapy in the management of cognitive PASC.

In the absence of alternative pathology, we recommend symptom monitoring, lifestyle optimization, and attention training for a period of six months. If symptoms persist at that time, we obtain formal neuropsychological testing for a baseline measure of cognition; determine the likelihood of alternative pathologies; and select targeted interventions with the assistance of occupational or speech and language therapists. A formal neurological evaluation should be considered for any patient who does not present with typical symptoms, has ongoing progression of symptoms following the acute infection, or has focal examination or imaging findings.

CONCLUSION

Mild SARS-CoV-2 infection is associated with a prolonged neurocognitive syndrome of impaired executive function in as many as 20% of cases. The chief complaint and major symptoms expressed may vary between patients as a function of their premorbid status and lifestyle. There is no recommended pharmacotherapy at this time, and treatment focuses on establishing an individualized cognitive rehabilitation regimen and excluding or treating other comorbid conditions that may impair cognition.

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Long-term Orthopedic Manifestations of COVID-19: Heterotopic Ossification and Digital Necrosis

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ABSTRACT

Despite its classification as an atypical pneumonia, COVID-19 is a disease that is capable of inflicting damage beyond the respiratory system. The wide range of musculoskeletal complications secondary to acute COVID-19 are a significant source of morbidity in hospitalized patients. We present the case of a 23-year-old woman with severe COVID-19 who required intubation and had a prolonged hospital course that was complicated by partial-thickness necrosis of her fingers and heterotopic ossification of the distal thigh. We review current treatments for these orthopedic conditions in the setting of SARS-CoV-2 infection as well as highlight areas for future research. Additionally, we discuss the subacute musculoskeletal complications of COVID-19, which are among the most common long-term manifestations of the disease and are increasingly important for a growing number of COVID-19 survivors.

KEYWORDS: COVID-19; orthopedic; heterotopic ossification; digital necrosis

INTRODUCTION

In late 2019, the first cases of the novel coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China.[1] Since then, the disease has become a worldwide pandemic resulting in hundreds of millions of cases and more than 6 million deaths.[2] Although initial attention focused primarily on the respiratory ramifications of the disease, COVID-19 is now recognized as a multi-system disease that can cause potentially devastating complications and long-term dysfunction throughout the body.

A variety of musculoskeletal complications related to both acute and post-acute sequelae of COVID-19 (PASC, also known as "Long COVID") have been reported.[3,4] These complications may in part be explained by the presence of angiotensin-converting enzyme 2 (ACE-2), the virus's major entry receptor, on skeletal muscle, synovial tissue, and the endothelium of small vessels.[5,6] Additionally, the widespread and prolonged inflammatory response as well as a prothrombotic state triggered by SARS-CoV-2 infection probably plays a role. We present a patient with severe COVID-19 who required intensive care unit (ICU) admission and mechanical ventilation. Her case was further complicated by heterotopic ossification of the distal thigh and digital necrosis. Additionally, we review other frequently reported musculoskeletal complications of COVID-19 illness and treatment both in the acute and subacute settings.

CASE REPORT

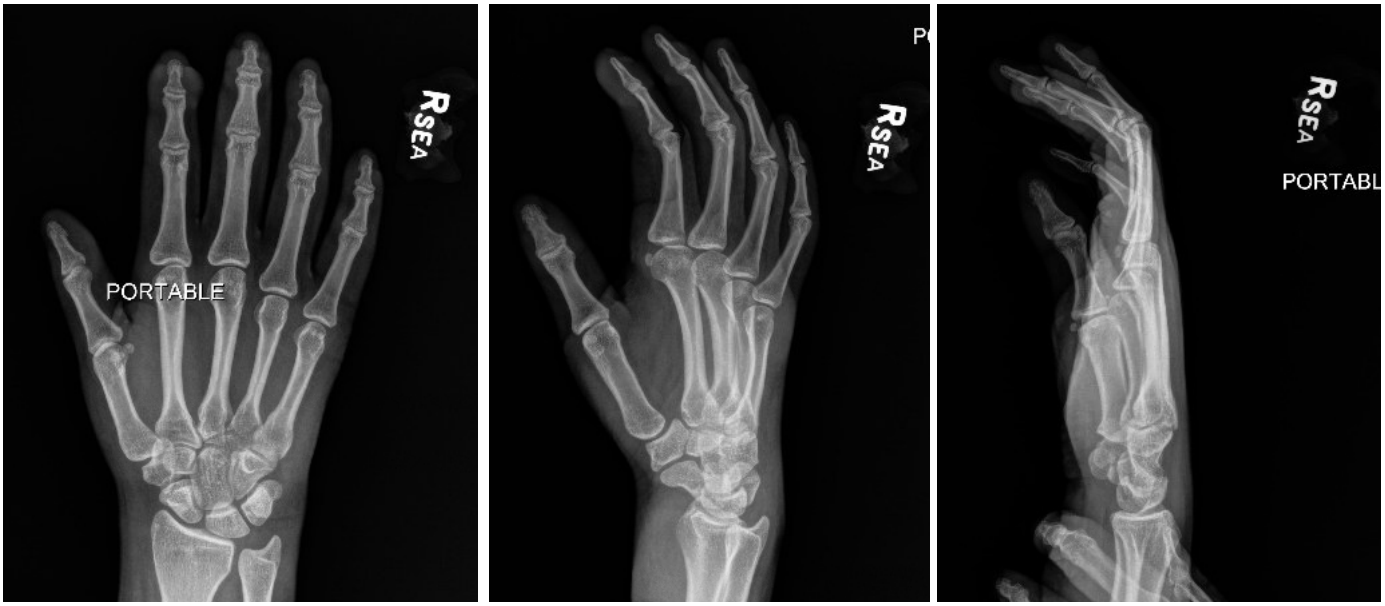
A 23-year-old-woman (unvaccinated against SARS-CoV-2) was admitted with shortness of breath and weakness due to COVID-19, after a normal vaginal delivery five days previously. A computed tomography angiogram (CTA) of her chest demonstrated pneumomediastinum, a segmental filling defect in the left lower pulmonary artery, and diffuse ground-glass opacities consistent with COVID-19 pneumonia. She was admitted to the intensive care unit and intubated for persistent respiratory distress. Her 81-day hospital course was complicated by refractory hypoxemia treated with venovenous extracorporeal membrane oxygenation (VV ECMO), pneumomediastinum, subsegmental pulmonary emboli, and disseminated intravascular coagulation managed with cryoprecipitate transfusions.

This patient also experienced orthopedic complications, and on hospital day 38 the Orthopedic Hand Service was consulted for partial thickness necrosis and dry eschars of the nail and dorsal fingertips distal to the distal interphalangeal joint (DIP) of the right index, middle, and ring fingers (**Figure 1a**). No acute findings were evident on plain radiographs (**Figures 2a-c**). The physical exam was limited due to the patient's intubated status. She had signals via Doppler ultrasound at the radial and ulnar arteries as well as her deep and superficial palmar arches. Her partial thickness digital necrosis was managed conservatively with therapeutic IV heparin and partial amputations were planned in the event of infections. Upon extubation, re-examination revealed that she had intact motor and sensory function of her right hand. The patient's skin findings continued to improve, with progressive resolution of the area of dry eschar (**Figure 1b**).

She was evaluated and followed by occupational therapy for upper extremity strength and range of motion (ROM) training and activities of daily living (ADL) training throughout her hospital course.

Figures 1a,b. Clinical photograph of dorsal right hand showing index, middle, and ring finger partial thickness necrosis at presentation (a), and clinical photograph of dorsal right hand 1 month later with interval improvement with conservative therapy and wound care (b).

Figures 2a-c. 3-view plain radiographs of right hand including anterior-posterior (AP) (a), oblique (b), and lateral (c) views, showing no acute fractures or bony pathology.



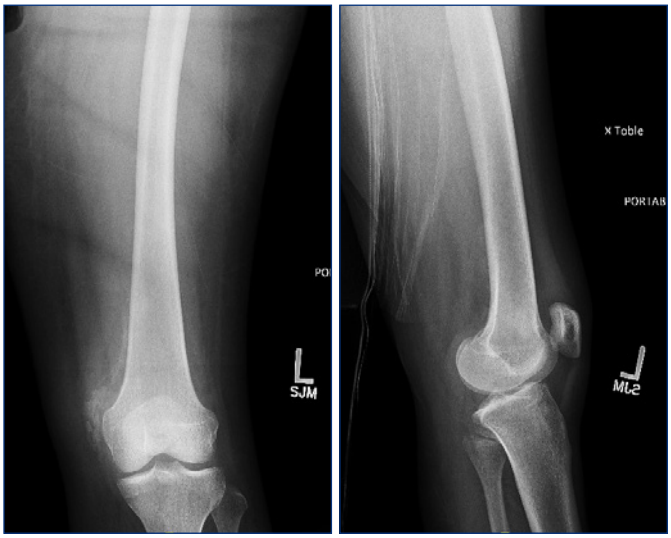
Several weeks after the appearance of her partial thickness digital necrosis, the Orthopedic Service was consulted for atraumatic left medial knee pain. She had a palpable, firm, non-fluctuant mass at the left distal medial thigh and both active and passive motion of the left knee were limited by pain. Radiographs and computed tomography (CT) scans demonstrated heterotopic ossification of the left vastus medialis (**Figures 3a,b; Figures 4a-c**). She was treated with nonsteroidal anti-inflammatories for pain control and physical therapy. She was seen by physical therapy throughout her hospital course for strength and range of motion (ROM) training as well as gait training, with nearly full resolution of her knee ROM. She was discharged to an acute rehabilitation center to facilitate recovery of her strength, flexibility, and functional independence. At two months after discharge, she had regained lower extremity strength and ROM, was able to ambulate with assisted devices, and had achieved independence with functional mobility.

DISCUSSION

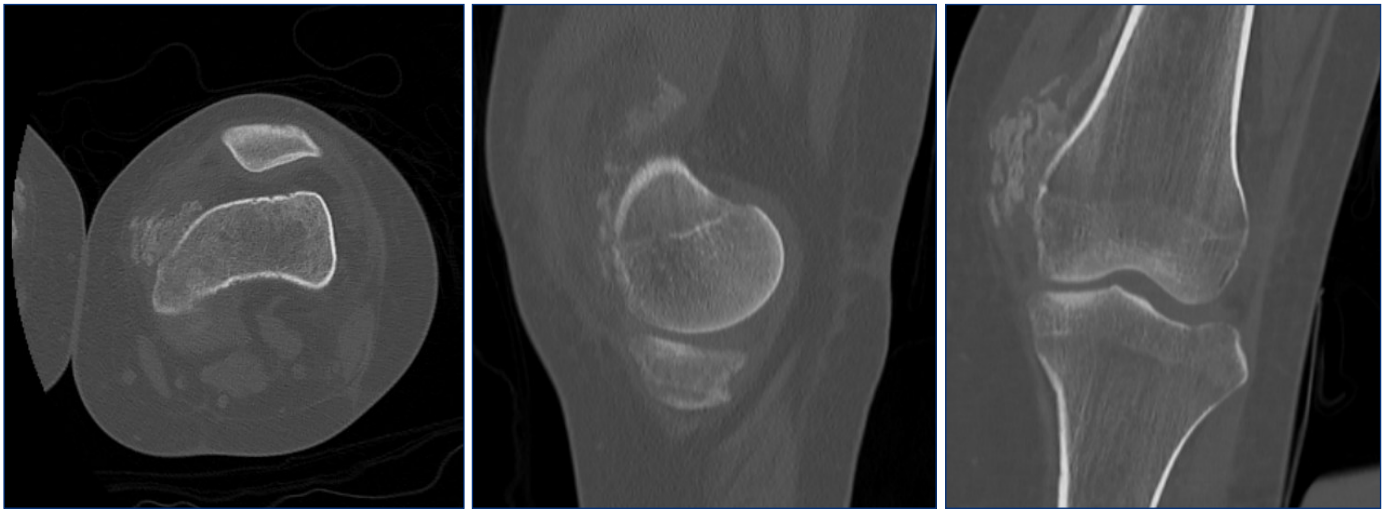
Early in the pandemic, COVID-19 was characterized as an atypical pneumonia, but it is better understood as a multi-system disease, as exemplified by our case of a 23-year-old woman with severe COVID-19 whose prolonged hospital course was complicated by heterotopic ossification and digital necrosis.

Endothelial dysfunction, inflammatory cytokine release, and hypoxia trigger decreased production and increased consumption of naturally occurring anticoagulants during severe

Figures 3a,b. Plain radiographs of distal femur with anterior-posterior (AP) (a) and oblique views (b), showing radio-opaque density suggestive of heterotopic ossification.



Figures 4a-c. Computed tomography (CT) scan of right distal femur with axial (a), sagittal (b), and coronal (c) views characterizing the extent of heterotopic ossification.



viral infection.[7] In COVID-19, direct endothelial injury from the SARS-CoV-2 virus via the ACE2 receptor may further exacerbate the coagulopathy.[8] The prothrombotic state can result in macrovascular as well as microvascular complications, such as the partial thickness digital necrosis seen in our patient.[7] Of note, digital necrosis is also well-described in patients requiring vasopressors and ICU-level care.[9,10] Thus, the exact etiology of acral necrosis in the setting of COVID-19 is likely multi-factorial and incompletely understood. Purpura, the cutaneous pattern that precedes digital gangrene in many of the reported cases, is characteristic of an occlusive micro-thrombotic process.[10,11] The preservation of major peripheral pulses in many cases also suggests a microvascular etiology.[9,12] Freeman et al analyzed six acral retiform purpura or necrotic lesions associated with COVID-19. The histopathology demonstrated non-inflammatory to pauci-inflammatory thrombi, leading the authors to conclude that acral necrosis is a cutaneous manifestation of the hypercoagulable state in COVID-19 patients.[10] However, poor responses to anticoagulation regimens have been reported in several cases of acral ischemia associated with COVID-19, prompting hypotheses that other processes such as neutrophil extracellular traps (NETs) or cold-sensitive antibody/immunoglobulin responses to the virus may play a role in the pathology.[12,13]

No standardized protocol exists for treatment for COVID-19-associated digital necrosis. The most common treatment reported in the literature is early and aggressive anticoagulation.[9,12] Further investigation is needed to determine if targeted immunotherapy or pharmaceutical agents dissolving NETs prove effective in treating digital ischemia unresponsive to anti-coagulation therapy. In the majority of reported digital necrosis cases, patients responded to conservative management, including wound care and anti-coagulation, or they died from other effects of COVID-19; however, Morales-Perez et al presented a case of surgical reconstruction of a necrotic thumb as well as a review of digital reconstruction in the setting of microvascular disease.[14]

In addition to digital necrosis, patients with severe COVID-19 are also at risk for heterotopic ossification (HO), a musculoskeletal complication characterized by ectopic formation of bone in soft tissues and around joints.[15,16] The exact mechanism of atraumatic HO remains unclear. It is thought to involve the differentiation of perivascular mesenchymal cells into osteoblasts when exposed to proinflammatory cytokines in the setting of altered local tissue factors, such as oxygen tension and pH.[16,17] In addition to the global inflammation experienced by COVID-19 patients, those requiring intubation are subject to prolonged

immobilization, another known risk factor for development of HO.[18,19] In fact, the reported cases of HO associated with COVID-19 have occurred exclusively in individuals who required mechanical ventilation.[20–24] In the largest series on the topic, Stoira et al retrospectively analyzed CT imaging of 52 intubated COVID-19 patients and found evidence of HO in ten (19%).[20]

Symptomatic HO presents most commonly as pain or loss of motion at a joint and has been reported around the hip, shoulder, or knee of COVID-19 patients requiring ICU level of care.[20–22] The diagnosis can be confirmed with radiographs; however, they have limited sensitivity early in the process.[17] Given the limited literature on HO with COVID-19 , treatment options are based on those utilized for HO secondary to neurologic insult or local trauma. NSAIDs, bisphosphonates, and radiation therapy are effective strategies to prevent HO in certain settings but no pharmaceutical treatment exists to address HO after it has formed.[17,18] NSAIDs can be utilized for prophylaxis and pain relief, but surgical removal remains the standard treatment when there is functional impairment and lack of improvement with conservative management including pain control and physical therapy.[17] The role of physical therapy in treating HO is a controversial topic. Historically, HO was considered a contraindication to range of motion exercises, based on the formation of ectopic bone in animal models subjected to aggressive stretching.[25,26] However, more recent research suggests that passive stretching may help preserve joint range of motion in patients with HO.[18,27] The optimal timing and types of physical therapy interventions have yet to be determined.

The musculoskeletal complications of COVID-19 are not limited to the acute effects of the disease and its treatment. In a long-term study of 285 patients, Karaarslan et al found that 40% of survivors had at least one musculoskeletal symptom six months post-infection, most commonly fatigue, joint pain, or myalgia.[4] A meta-analysis of persistent post-acute sequelae in more than 250,000 survivors found similar rates of muscle weakness.[28] Although critical illness myopathy is a well-documented consequence of ICU treatment for COVID-19 and other diseases, myopathic changes have also been documented in patients with mild COVID-19 infection, suggesting a different etiology in some cases.[29,30] Proposed mechanisms for post-acute muscle weakness include viral infiltration into skeletal muscle or muscle damage secondary to an aberrant immune response.[31] Physical activity has proven a powerful tool for preventing and improving myopathy associated with long-term COVID-19.[1,31] Rehabilitation should begin as soon as sedation and clinical stability allow; previous studies have demonstrated the feasibility and benefits of ambulation in ICU patients.[32] Post-hospitalization, recovering patients should partake in exercise that balances strength and flexibility to improve their gait as well as regain muscle mass.[1] Exercise programs proven effective in restoring function in randomized controlled trials involving SARS-CoV-1 survivors could serve as helpful templates for current efforts to develop rehabilitation protocols.[33] Recent studies have also explored the role of neuromuscular electrical stimulation and vitamin D supplementation in preserving and recovering muscle function, although further research is needed to determine the effectiveness of these modalities.[34,35]

Despite increasing availability of vaccines and treatments for COVID-19, hundreds of thousands of new infections occur daily.[2] Questions about the pathogenesis and optimal treatment for COVID-19-associated musculoskeletal conditions, especially long-term effects, require continued investigation. Increased understanding of the orthopedic manifestations of the disease is critical to improving care for patients and minimizing the healthcare burden.

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