# RIMJ Special Section: The Evaluation & Rehabilitation of Long COVID

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## 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]

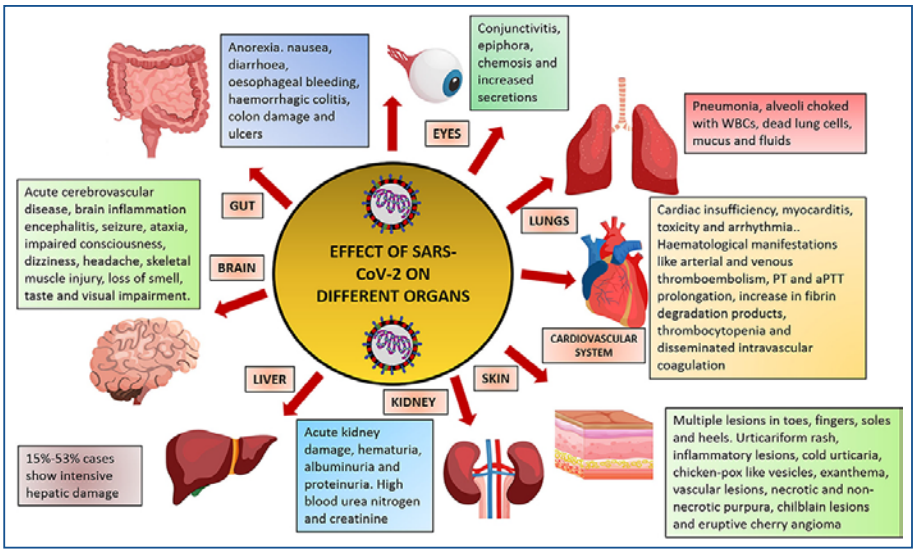
In view of the aggressive and invasive nature of the SARS-CoV-2 virus, which attacks multiple organ systems and causes a widespread inflammatory and pro-thrombotic state, it is not surprising that patients develop Long COVID (**Figure 2**). Furthermore, the lingering presence of the virus is associated 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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