Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

MAYO CLINIC

Post–COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the Initial Patient Cohort

Greg Vanichkachorn, MD, MPH; Richard Newcomb, MD, MPH; Clayton T. Cowl, MD, MS; M. Hassan Murad, MD, MPH; Laura Breeher, MD, MPH; Sara Miller, APRN, CNP; Michael Trenary, PT, DPT; Daniel Neveau, MA, OTR/L; and Steven Higgins, PT, DPT

Abstract

Objective: To describe characteristics of a series of patients reporting prolonged symptoms after an infection with coronavirus disease 2019 (COVID-19).

Patients and Methods: This study describes the multidisciplinary COVID-19 Activity Rehabilitation Program, established at Mayo Clinic to evaluate and treat patients with post–COVID syndrome, and reports the clinical characteristics of the first 100 patients receiving evaluation and management during the timeframe of June 1, 2020, and December 31, 2020.

Results: The cohort consisted of 100 patients (mean age, 45.4±14.2 years; 68% women; mean body mass index, 30.2 kg/m^2; presenting a mean of 93 days after infection). Common preexisting conditions were respiratory (23%) and mental health, including depression and/or anxiety (34%). Most (75%) had not been hospitalized for COVID-19. Common presenting symptoms ware fatigue (80%), respiratory complaints (59%), and neurological complaints (59%) followed by subjective cognitive impairment, sleep disturbance, and mental health symptoms. More than one-third of patients (34%) reported difficulties in performing basic activities of daily living. Only 1 in 3 patients had returned to unrestricted work duty at the time of the analysis. For most patients, laboratory and imaging tests showed no abnormalities or were nondiagnostic despite debilitating symptoms. Most patients required physical therapy, occupational therapy, or brain rehabilitation. Face-to-face and virtual care delivery modalities were feasible.

Conclusion: Most of the patients did not have COVID-19–related symptoms that were severe enough to require hospitalization, were younger than 65 years, and were more likely to be female, and most had no preexisting comorbidities before severe acute respiratory syndrome coronavirus 2 infection. Symptoms including mood disorders, fatigue, and perceived cognitive impairment resulted in severe negative impacts on resumption of functional and occupational activities in patients experiencing prolonged effects.

 ■ Mayo Clin Proc. 2021;96(7):1782-1791

From the Division of Preventive, Occupational, and Aerospace Medicine (G.V., R.N., C.T.C., M.H.M., L.B., S.M.) and

Affiliations continued at the end of this article.

By March 2021, an estimated 28.6 million Americans in the United States have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), with more than 500,000 deaths.[1] Although efforts to vaccinate large populations globally are ongoing and the numbers of new cases have declined in some regions of the world, a wide variation in the spectrum of clinical symptoms has been documented for those infected previously—from asymptomatic individuals testing positive for the virus to

Mayo Clin Proc. ■ July 2021;96(7):1782-1791 ■ https://doi.org/10.1016/j.mayocp.2021.04.024
www.mayoclinicproceedings.org ■

others with rapidly progressive symptoms requiring hospitalization and mechanical ventilation and who may later have respiratory failure and/or death.[2,3] Advanced age, ethnicity, sex, race, elevated body mass index (calculated as the weight in kilograms divided by the height in meters squared), immunosuppression, and other medical comorbidities have been described as risk factors for severe infections requiring hospitalization.[1,4-6] Although considerable epidemiological data have been published for individuals who have severe symptoms requiring inpatient care, the natural history and symptom patterns for patients with COVID-19 who do not require hospitalization is just beginning to be described.[7]

Prolonged symptoms have been recognized as affecting individuals in previous epidemics, such as with the coronavirus causing severe acute respiratory syndrome (SARS) outbreaks in 2003. One-third of patients surviving SARS had chronic dyspnea and other respiratory symptoms exceeding 12 months after acute infection.[8] In addition, radiographic abnormalities suggesting pulmonary fibrotic change were identified in 45% of patients 1 month after infection, 30% to 36% at 3 to 6 months, and 28% within 1 year of the initial infection.[9] Moreover, nonpulmonary symptoms persisted, such as headaches, anxiety, depression, and myalgias.

Several studies have described patients with COVID-19 and prolonged symptoms, tracking individuals who remained hospital confined or who were dismissed to the outpatient setting after being hospitalized. In Italy, 143 hospitalized patients were surveyed approximately 60 days after symptom onset, with 32% reporting persistence of at least 1 to 2 symptoms and 55% having 3 or more. The most common symptoms were fatigue and dyspnea.[10] Similarly, a Parisian study of 120 patients interviewed on average 111 days after acute infection revealed most had some form of lingering symptoms including fatigue (55%), dyspnea (42%), perceived cognitive difficulties (34%), and sleep disorders (31%).[11] Headache has been the most common neurological complaint (14%),[8] along with other nonspecific subjective symptoms of concentration difficulties, subjective memory loss, reduced attention span, and even delirium, the latter noted predominantly in hospitalized populations.[12-16]

Longer-term sequelae of SARS-CoV-2 infection involving outpatients have not been described as thoroughly. A recent longitudinal prospective cohort study[17] tracked chronic symptoms in a cohort of 234 patients who had COVID-19 residing in the Pacific Northwestern United States. Outcomes 9 months after laboratory-confirmed SARS-CoV-2 infection suggested that 30% of individuals were having 1 or more symptoms persisting 9 months or longer, including 13.6% affected by generalized fatigue, another 13% with anosmia, and 13% reporting other more nebulous symptoms such as "brain fog." Symptoms were more likely to be prolonged in older age groups.

A multidisciplinary clinic at Mayo Clinic's campus in Rochester, Minnesota, was developed to provide comprehensive care to individuals who had COVID-19 having persistent symptoms. In this report, we outline the components and approach of this clinic and describe the initial 100 patients participating in this program. This report describes a self-referred population of patients with laboratory-confirmed SARS-CoV-2 infection who had COVID-19 and reported persistent symptoms spanning 1 to 6 months, often referred to as "post-COVID syndrome" (PCS) or "COVID long haul syndrome" or "long haul COVID-19."

PATIENTS AND METHODS

Program Description

As patients with COVID-19 recovering from acute illness in the spring of 2020 were recorded, many survivors of severe disease reported difficulties returning to their baseline function. In addition, patients with less severe COVID-19 were noted to have lingering and multiple symptoms even though sequential nasopharyngeal swab testing for SARS-CoV-2 had become negative. Initial efforts to assess, characterize, and treat these individuals began with an

informal multidisciplinary team that collaborated first in April 2020. As the number of patients requesting assistance increased, by June 2020 this team was transitioned into a more structured clinic referred to as the COVID-19 Activity Rehabilitation Program (CARP). The program interventions were based on treatments used for SARS/Middle East respiratory syndrome (MERS) and chronic fatigue syndrome, recommendations by a pool of health care professionals practicing within various specialty fields focused on prevention, diagnostics, and rehabilitation, as well as the limited available data published on recovery from patients with COVID-19 worldwide.

The Mayo Clinic program was delivered via face-to-face visits and/or virtually by using either video telemedicine or telephone interactions. Although there was no limit on how soon patients could establish care in the clinic after infection, no CARP interventions were performed until at least 4 weeks after a positive SARS-CoV-2 polymerase chain reaction (PCR) test and/or symptomatic start of confirmed SARS-CoV-2 infection.

There are 3 primary objectives of CARP. The first has been to actively assess for any associated conditions and to detect evidence for decompensation in the early recovery phase. A Michigan study of 1250 patients initially hospitalized with COVID-19 found that 84 patients had died within 60 days of discharge. The fatality rate was higher in patients who had been admitted to an intensive care unit (10.4%) than in those who were not (6.7%).[18] In addition, thromboembolic complications, such as deep vein thrombosis, pulmonary embolism, and acute ischemic stroke, have been associated with SARS-CoV-2 infection, with pulmonary embolism being the most common.[19,20]

The second objective has been to facilitate improvement in function. This is primarily achieved through physical and occupational therapy, focusing therapy as a customized individually paced program, vs a stepwise graded activity approach standardized for each individual enrolled. This approach has been based on therapeutic outcomes recorded during the SARS epidemic as well as treatment pathways used to address individuals having myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and is described in more detail below.[21-23] Physical therapy begins with an assessment of vital signs (blood pressure, heart rate, and oxygen saturation) and a 6-minute walk test. These data, along with perceived exertion and dyspnea, help guide the initial activity recommendations, which involve development of a general strengthening and conditioning program. Reestablishing self-care routines, in particular optimizing sleep hygiene, has been the role of occupational therapists who help patients concentrate on daily structure, tempering efforts to return to full activity immediately, and emphasizing individualized activity thresholds. Instructions on diaphragmatic breathing and relaxation techniques reduce the work of breathing, as well as reduce muscle tension, and assist in stress management. Psychosocial-based treatment, by both physical therapy and occupational therapy, is used to identify and remove unique barriers to recovery and help reformulate preconceived notions of illness and disability. Job-specific testing and simulations are used to help guide appropriate work restrictions, which are managed, for the most part, by occupational medicine specialists.

The third objective is to facilitate a therapeutic and safe pathway for returning to work. Management of work restrictions is often an intensive process during which the provider must obtain a detailed understanding of the patient's occupation while weighing the impairing medical condition and taking into account factors such as perceived pain, symptom magnification, catastrophizing, the patient's education level, employment rank, and fear of reinjury.[24] Management of these variables requires trust by the patient, careful communication, and role clarity among multiple stakeholders, including employers, legal representatives, and insurance adjusters, in addition to the patient.[24] To meet these unique demands,

Mayo Clin Proc. ■ July 2021;96(7):1782-1791 ■ https://doi.org/10.1016/j.mayocp.2021.04.024
www.mayoclinicproceedings.org

CARP was staffed primarily by occupational medicine specialists, who have received specific training to navigate this intricate process and opine on work injury risk, tolerance, and capacity. The physical/occupational therapy component used by CARP was also adapted from the treatment of injured workers, in which psychosocial-focused treatment is crucial for recovery.[25] Typical tests and consultations used in CARP are described in Table 1. Routine laboratory work was performed to assess for infection, electrolyte abnormalities, and renal or hepatic dysfunction. Vitamin B_{12} and vitamin D levels were obtained to assess deficiencies. Thyroid-stimulating hormone was drawn to check for fatigue related to undiagnosed hypothyroidism. To assess respiratory function, chest radiography and spirometry were frequently performed. Complications of thromboembolic disease were assessed by lower extremity Doppler ultrasound, serum D-dimer levels, and computed tomography angiogram of the chest. Autonomic nervous system dysfunction, including orthostatic intolerance and sudomotor dysfunction, was assessed using an autonomic reflex screen. Finally, functional ability was measured using either a 6-minute walk test or a cardiopulmonary exercise test.

TABLE 1. COVID-19 Activity Rehabilitation Program Elements

Function focused interview	Assess for: • Fatigue • Dyspnea • Depression/anxiety • Brain fog • BP/HR fluctuations • Sleep quality • Appetite • Signs of pulmonary embolism/DVT Review of preexisting conditions Ability with ADLs and IADLS Pre—COVID-19 functional status Complete occupational history Identification of patient's treatment goals
Standard laboratory assessments	CBC CMP Vitamin D Vitamin B_{12} Thyroid-stimulating hormone
Optional diagnostic tests	Chest radiography Echocardiography Pulmonary function test Lower extremity Doppler D-Dimer Computed tomography angiography of the chest Autonomic reflex testing 6-Minute walk test Cardiac stress test Cardiopulmonary exercise test
Optional consultations	Pulmonary Infection disease Cardiology Brain rehabilitation Chronic fatigue Neurology Psychiatry Employee assistance program Physical/occupational therapy Speech therapy Autonomic patient education

ADL, activity of daily living; BP, blood pressure; CBC, complete blood count, CMP, comprehensive metabolic panel; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; HR, heart rate; IADL, instrumental activities of daily living.

Case Definition

Currently, there is no universal definition or label for the prolonged symptoms that may occur after having COVID-19. The term PCS was first chosen by the CARP team in June 2020 because it best described the wide variety of chronic symptoms reported in the literature describing these groups. Since then, the National Institutes of Health has coined the term "post—acute sequelae of SARS-CoV-2." The COVID-19 Activity Rehabilitation Program refers to the constellation of usual symptoms as PCS, whereas post—acute sequelae of SARS-CoV-2 is used to refer to any symptoms after SARS-CoV-2 infection, such as solitary cough. A working definition of PCS to help guide eligibility criteria for CARP was as follows:

1. presence of symptoms attributed to SARS-CoV-2 infection continuing 4 or more weeks after either a positive COVID-19

PCR test or symptomatic start of a clinically diagnosed SARS-CoV-2 infection (the basis for this decision was evidence that most patients with COVID-19 in the community recovered within 2-3 weeks[26]) and
2. a positive COVID-19 PCR or SARS-CoV-2 antibody (serology) test.

Additional inclusion criteria for the treatment program included age 18 years and older and having either a positive COVID-19 PCR test or symptomatic start of a clinically diagnosed SARS-CoV-2 infection within 6 months of evaluation.

Data Collection and Analysis

Institutional Review Board approval was obtained before data collection, which was deemed minimal risk. A database of patients with PCS was created that included all patients who had been evaluated in the CARP clinic. Randomized numerical aliases were generated for each patient before data abstraction from the medical record. No patient identifier information was collected or stored in the research database.

Patients who had a complete symptomatic recovery from acute SARS-CoV-2 infection less than 4 weeks from the start of symptoms and/or positive PCR test date were excluded from the database, as well as patients who did not have a laboratory-confirmed COVID-19 PCR or SARS-CoV-2 antibody test result in the medical record.

To minimize variation, data abstraction was performed by a single team member by using a standardized intake log. As an exploratory program, detailed patient interviews were used for initial visits; however, standardized surveys were not used systematically during evaluation or treatment. Hospitalization history, most recent body mass index, and treatment course were determined primarily by abstraction of the electronic health record, which included documentation in clinical notes as reported by patients. The presence of pre—COVID-19 cardiovascular or respiratory conditions, fibromyalgia, chronic fatigue syndrome, diabetes, and mental health conditions were assessed through pre—COVID-19 medical record review and patient-reported history.

Presenting symptoms were recorded from clinical documentation. *Cognitive symptoms* were defined as any subjective reports of concentration difficulty, perceived memory loss, word finding difficulty, and inability to effectively multitask. *Neurological symptoms* were defined as subjective complaints of paresthesia, headache, dizziness, tachycardia, and/or labile vital signs (ie, fluctuating heart rate or blood pressure). The *presence of psychiatric symptoms* was defined as increased severity of depressed mood or anxiety when compared with the individual clinical status before their SARS-CoV-2 infection. *Activities of daily living* (ADLs) were defined broadly as basic activities of life, such as toileting and grooming. Occupational information was obtained from patient-reported history. A *patient* was defined as previously employed if they were working at the time of their acute SARS-CoV-2 infection. *Return to work* was defined as working in any capacity, including reduced hours or accommodated functional activities, at their usual work site or an alternative location such as home (telework). *Full duty work* was defined as return to pre—COVID-19 work hours and essential functions of the job. The frequency of tests, such as echocardiography, and the corresponding results were abstracted from the electronic medical record. Data are presented using descriptive statistics.

RESULTS

Patient Characteristics

We report on the first 100 patients with PCS participating in CARP. Table 2 summarizes the demographic characteristics, comorbidities, and presenting symptoms. The mean age of patients seeking care in CARP was 45.4±14.2 years, and most were female (68%). Most patients in CARP presented about 3 months after the diagnosis of SARS-CoV-2 infection (93.4±65.2 days), and most had the infection confirmed via the nucleic acid amplification PCR test (93%).

Mayo Clin Proc. ■ July 2021;96(7):1782-1791 ■ https://doi.org/10.1016/j.mayocp.2021.04.024
www.mayoclinicproceedings.org

The most common preexisting condition category was respiratory (23%), with asthma being the most prevalent diagnosis. Other preexisting conditions included a history of depression or anxiety (34%), hypertension (19%), chronic fatigue syndrome (4%), and diabetes (3%). Most patients (75%) had not been hospitalized for SARS-CoV-2 infection. The mean body mass index of the cohort was 30.2±7.8 kg/m^2.

The most common symptom noted on initial presentation to the program was fatigue (80%), followed by respiratory complaints (59%) and neurological complaints (59%). The most common respiratory symptom was dyspnea (49%), and the most common neurological symptom was headache (20%). Other common symptoms were subjective cognitive complaints, sleep disturbance, and mental health symptoms. Altered taste/smell was an infrequent prolonged symptom in the cohort. Functionally, more than one-third (34%) of patients in CARP reported having difficulties in performing ADLs and 84% of patients reported trouble with household chores, exercise, driving, and/or completing tasks required at work.

TABLE 2. Patient Characteristics (N=100)[a,b]

Characteristic	Value
General and demographic characteristics	
Age (y)	45.4±14.2
Female sex	68.0 (n=68)
Body mass index (kg/m^2)	30.2±7.8
Time to presentation (d)	93.4±65.2
Positive PCR test	93 (n=93)
Positive antibody test only	8 (n=8)
Not hospitalized	75 (n=75)
Preexisting conditions	
With existing respiratory conditions	23 (n=23):
	Asthma (n=14)
	OSA (n=8)
	COPD (n=1)
With existing cardiac conditions	22 (n=22):
	Hypertension (n=19)
	CHF/cardiomyopathy (n=3)
	Pericarditis (n=1)
With existing depression/anxiety	34 (n=34)
With existing type 1 or 2 diabetes mellitus	5 (n=5)
With existing myalgic encephalomyelitis/chronic fatigue syndrome	4 (n=4)
Presenting symptoms	
Fatigue	80 (n=80)
Respiratory complaints	59 (n=59):
	Dyspnea (n=49)
	Cough (n=15)
Neurological complaints	59 (n=59):
	Headache (n=20)
	Dizziness (n=19)
	Paresthesia (n=17)
	Labile vital signs (n=7)
Cognitive impairment	45 (n=45)
Sleep disturbance	30 (n= 30)
Mental health symptoms	26 (n=26)
Persistent altered taste/smell	9 (n=9)
Hair loss	6 (n=6)
Limits with ADLs	34 (n=34)
Limits with normal function	82 (n=82)

[a]ADL, activity of daily living; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; PCR, polymerase chain reaction.
[b]Data are presented as mean ± SD or as percentage.

Occupational Data

With the primary goal of restoring function and returning to work, occupational data were collected and tabulated in Table 3. Before their infection, 91% of the cohort was employed and 63 patients had returned to some form of gainful employment at the time of presentation to CARP. However, of the 63 patients who had returned to work, only 46% had returned to unrestricted work duty at the time of presentation to CARP. At initial intake, 31% of employed patients (28 of 91 patients) had not returned to work in any capacity after their SARS-CoV-2 infection. Table 3 also describes several differences between those who return to full-time unrestricted work duty and the remainder of the patients.

Diagnostics, Referrals, and Therapies

Diagnostic testing volumes are outlined in Table 4. Interestingly, most tests were within normal limits. Two of 31 echocardiograms were described as abnormal, revealing reduced ejection fraction and mild ventricular dysfunction. Only a few patients had abnormalities of spirometry or decreased diffusing capacity for carbon monoxide. No potentially life-threatening conditions, such as pulmonary thromboembolic disease,

TABLE 3. Occupational Characteristics[a,b]

Work status	Work status	Cognitive complaints	Anxiety/ depression	Sleep disturbance	Limits with ADLs	Limits with normal function	Time to presentation (d)
No work	31.0 (n=31)	38.7 (n=12)	29.0 (n=9)	35.5 (n=11)	48.4 (n=15)	90.3 (n=28)	109.5±7.9
Work in any form	63.0 (n=63)	46.0 (n=29)	27.0 (n=17)	28.6 (n=18)	25.3 (n=16)	77.8 (n=49)	88.9±5.5
Full duty work	46.0 (n=29/ 63)	37.9 (n=11)	34.5 (n=10)	27.6 (n=8)	20.7 (n=6)	75.9 (n=22)	81.7±8.1

[a]ADL, activity of daily living.
[b]Data are presented as percentage.

were identified. There were sporadic cases of positive acute (IgM) antibody titers for cytomegalovirus and Epstein-Barr virus, but seroconversion to IgG was seen in only 1 case. It is currently unclear whether the cytomegalovirus/Epstein-Barr virus tests represent reactivations with unknown clinical significance or a false-positive result due to changes in patient immune status.

DISCUSSION

This study describes the first 100 patients seen in one of the first multidisciplinary programs focused on PCS, also termed "long haul COVID-19." An important finding is that the population with PCS in CARP appears distinct from those who suffer from more severe cases of acute SARS-CoV-2 infection. Although advanced age and the presence of several comorbidities are positively associated with increased mortality and hospitalization during acute infections, patients in CARP were younger (mean age, 45.4±14.2 years) than groups associated with severe infection, high mortality, and hospitalization.[27] In addition, most patients with PCS had no relevant medical conditions before their SARS-CoV-2 infection, making it difficult to predict which patients may be at risk for PCS. It is also notable that female patients outnumbered male patients roughly 3:1, despite male sex being associated with poorer acute COVID-19 outcomes.[28] Female sex preponderance is seen with other post–viral syndromes.[29] Unfortunately, this descriptive study does not include enough data to hypothesize for this sex difference.

TABLE 4. Therapy, Referral, and Diagnostic Use[a,b]

Treatment/test	Value
Physical therapy	42 (n=42)
Occupational therapy	27 (n=27)
Pulmonary consultation	27 (n=27)
Brain rehabilitation consultation	22 (n=22)
Infectious disease consultation	6 (n=6)
Chest radiography	34 (n=34)
Spirometry with DL_{CO}	27 (n=27)
Transthoracic echocardiography	29 (n=29)
Autonomic reflex testing	20 (n=20)

[a]DL_{CO}, diffusing capacity for carbon monoxide.
[b]Data are presented as percentage.

Consistent with other studies, fatigue and dyspnea were the most common complaints seen in CARP. However, self-reported cognitive difficulty, anxiety, depression, and insomnia were also common. Patients reported that their cognitive and mood symptoms were often minimized or dismissed by health care providers, which is concerning because many PCS symptoms are similar to prolonged sequela after traumatic brain injury for which prolonged or permanent inability to return to work has been recorded.[30-32] As an initial observational study, it is too early to determine the full impact of symptoms and treatment on an individual's ability to return to work. However, the results do provide impetus for a thorough assessment and consideration of all symptoms and their impact on functional capacity both at work and at home. Patient and provider concern for PCS impact on ADLs and work was common in this

Mayo Clin Proc. ■ July 2021;96(7):1782-1791 ■ https://doi.org/10.1016/j.mayocp.2021.04.024
www.mayoclinicproceedings.org

initial cohort, noting that the prolonged average time to presentation being roughly 3 months after acute infection is troublesome as well as suggesting the presence of prolonged workplace absenteeism with PCS.

Patients in CARP underwent multiple tests, most of which were normal or nondiagnostic. This is in contrast with other published studies, which have reported a high prevalence of abnormal results, especially echocardiographic and cardiac magnetic resonance imaging data.[33] These findings underscore that diagnostic testing should be performed judiciously and that clinically significant symptoms may not be explained solely by diagnostic results. Autonomic testing was conducted in many patients in the program because of recorded labile vital signs and symptoms such as persistent tachycardia. Positional orthostatic tachycardia syndrome has been associated with ME/CFS, and there are already several case reports of COVID-19—related autonomic dysfunction.[34,35] At the time of publication, 15 patients had completed autonomic reflex testing, and 12 tests indicated abnormalities. These patients were referred to neurologists and, in some cases, offered propranolol and advised on other potential therapies such as adequate hydration and salt intake and use of compression garments.

In terms of treatments used in the program, brain rehabilitation was offered to some patients because of evidence suggesting that active recovery is more effective for concussion treatment as compared with complete physical and mental rest.[36,37] Physical/occupational therapy was frequently used because research from the SARS and MERS epidemics found that these modalities were associated with improvements in function.[23,38] In addition, research on both the SARS/MERS epidemics and ME/CFS indicates that in some post—viral syndromes, excessive activity can result in prolonged worsening of symptoms and function.[39,40] Finally, psychosocial support of patients was heavily emphasized. Patients in CARP frequently reported feelings of abandonment, guilt, and frustration during the initial evaluation, and 26% reported increased anxiety and depression symptoms compared with baseline before SARS-CoV-2 infection. Psychosocial support included referrals to counseling, use of employee assistance programs, and referral to psychiatrists or other mental health professionals.

The COVID-19 Activity Rehabilitation Program has focused on functional abilities that include returning to work, providing an opportunity for health care professionals to recognize the impact on this important social determinant of health in patients. This case series is limited in drawing any population-based conclusions involving patients with PCS because of its small initial sample size and the fact that this was a self-referred convenience sample. Although the initial cohort reported was predominantly female and younger than 45 years, this may represent a skewed sample in light of the setting of the Mayo Clinic CARP clinic being located in a health care setting with increased awareness of this clinical resource among health care personnel (ie, nurses struggling with PCS) compared with patients from other occupations and industries. The format of the program intake with an interview rather and a standardized intake questionnaire resulted in variability in data and could result in lack of full recognition of PCS symptoms or functional impact. In addition, the lack of a universal definition of PCS limits generalizability to a broader population.

CONCLUSION

This descriptive report provides an additional view on PCS. In this population of patients presenting to a multidisciplinary academic medical center, patients with PCS appear to be younger than individuals at high risk for hospitalization and mortality during acute SARS-CoV-2 infection. Most patients were not hospitalized, and less than one-third of patients had pre—COVID-19 cardiovascular, respiratory, or mental health conditions. In addition to fatigue and shortness of breath, many patients reported subjective mood symptoms,

sleep fragmentation, and perceived cognitive difficulties. Numerous patients have not been able to return to work in any capacity, and sometimes return to their previous occupation is delayed months after their initial SARS-CoV-2 infection. Many diagnostic tests were normal or nondiagnostic and should be used judiciously.

ACKNOWLEDGMENTS

We express our gratitude to the COVID-19 Frontline Care Team at Mayo Clinic for their assistance.

Abbreviations and Acronyms: **ADL** = activity of daily living; **CARP** = COVID-19 Activity Rehabilitation Program; **COVID-19** = coronavirus disease 2019; **ME/CFS** = myalgic encephalomyelitis/chronic fatigue syndrome; **MERS** = Middle East respiratory syndrome; **PCS** = post–coronavirus disease syndrome; **PCR** = polymerase chain reaction; **SARS** = severe acute respiratory syndrome; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2

Affiliations (Continued from the first page of this article.): Division of Physical Medicine and Rehabilitation (M.T., D.N., S.H.), Mayo Clinic, Rochester, MN.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Greg Vanichkachorn, MD, MPH, Division of Preventive, Occupational, and Aerospace Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Vanichkachorn.greg@mayo.edu).

ORCID

Greg Vanichkachorn: https://orcid.org/0000-0002-4483-5996; M. Hassan Murad: https://orcid.org/0000-0001-5502-5975; Laura Breeher: https://orcid.org/0000-0002-6327-5162

REFERENCES

1. COVID data tracker. Centers for Disease Conrol and Prevention website. https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed March 20, 2021.
2. Cardemil CV, Dahl R, Prill MM, et al. COVID-19-related hospitalization rates and severe outcomes among veterans from 5 Veterans Affairs medical centers: hospital-based surveillance study. *JMIR Public Health Surveill*. 2021;7(1):e24502.
3. Nemer DM, Wilner BR, Burkle A, et al. Clinical characteristics and outcomes of non-ICU hospitalization for COVID-19 in a nonepicenter, centrally monitored healthcare system. *J Hosp Med*. 2021;16(1):7-14.
4. Chang MH, Moonesinghe R, Truman BI. COVID-19 hospitalization by race and ethnicity: association with chronic conditions among medicare beneficiaries, January 1-September 30, 2020 [published online ahead of print January 8, 2021]. J Racial Ethn Health Disparities. https://doi.org/10.1007/s40615-020-00960-y.
5. Dai CL, Komilov SA, Roper RT, et al. Characteristics and factors associated with SARS-CoV-2 infection, hospitalization, and mortality across race and ethnicity [published online ahed of print February 20, 2021]. *Clin Infect Dis*, https://doi.org/10.1093/cid/ciab154.
6. Telle KE, Grøsland M, Helgeland J, Håberg SE. Factors associated with hospitalization, invasive mechanical ventilation treatment and death among all confirmed COVID-19 cases in Norway: prospective cohort study. *Scand J Public Health*. 2021;49(1):41-47.
7. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232.
8. Barker-Davies RM, O'Sullivan O, Senaratne KPP, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. *Br J Sports Med*. 2020;54(16):949-959.
9. Yang LL, Yang T. Pulmonary rehabilitation for patients with coronavirus disease 2019 (COVID-19). *Chronic Dis Transl Med*. 2020;6(2):79-86.
10. Carfì A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605.
11. Garrigues E, Janvier P, Kherabi Y, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*. 2020;81(6):e4-e6.
12. Baker HA, Safavynia SA, Evered LA. The 'third wave': impending cognitive and functional decline in COVID-19 survivors. *Br J Anaesth*. 2021;126(1):44-47.
13. André A, Félix C, Nzwalo H. Should we mind for late neurologic manifestations from novel coronavirus? *Clin Neurol Neurosurg*. 2020;196:106021.
14. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
15. Tsai ST, Lu MK, San S, Tsai CH. The neurologic manifestations of coronavirus disease 2019 pandemic: a systemic review. *Front Neurol*. 2020;11:498.
16. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol*. 2020;77(8):1018-1027.
17. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after SARS-CoV-2 infection. *JAMA Netw Open*. 2021;4(2):e210830.
18. Chopra V, Flanders SA, O'Malley M, Malani AN, Prescott HC. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann Intern Med*. 2021;174(4):576-578.
19. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with influenza. *JAMA Neurol*. 2020;77(11):1-7.
20. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147.
21. Wang TJ, Chau B, Lui M, Lam GT, Lin N, Humbert S. Physical medicine and rehabilitation and pulmonary rehabilitation for COVID-19. *Am J Phys Med Rehabil*. 2020;99(9):769-774.
22. Geraghty K, Hann M, Kurtev S. Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: analysis of a primary survey compared with secondary surveys. *J Health Psychol*. 2019;24(10):1318-1333.
23. Lau HM, Ng GY, Jones AY, Lee EW, Siu EH, Hui DS. A randomised controlled trial of the effectiveness of an exercise training program in patients recovering from severe acute respiratory syndrome. *Aust J Physiother*. 2005;51(4):213-219.
24. Macías-Toronjo I, Sánchez-Ramos JL, Rojas-Ocaña MJ, García-Navarro EB. Influence of psychosocial and sociodemographic variables on sickness leave and disability in patients with

work-related neck and low back pain. *Int J Environ Res Public Health*. 2020;17(16):5966.
25. Besen E, Young AE, Shaw WS. Returning to work following low back pain: towards a model of individual psychosocial factors. *J Occup Rehabil*. 2015;25(1):25-37.
26. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020; 323(13):1239-1242.
27. Risk for SARS-CoV-2 infection, hospitalization, and death by age group. Centers for Disease Conrol and Prevention website. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed March 20, 2021.
28. Park R, Chidharla A, Mehta K, Sun W, Wulff-Burchfield E, Kasi A. Sex-bias in COVID-19-associated illness severity and mortality in cancer patients: a systematic review and meta-analysis. *EClinicalMedicine*. 2020;26:100519.
29. Straus SE, Tosato G, Armstrong G, et al. Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. *Ann Intern Med*. 1985;102(1):7-16.
30. Lian Y, Xiao J, Liu Y, et al. Associations between insomnia, sleep duration and poor work ability. *J Psychosom Res*. 2015; 78(1):45-51.
31. Bergman E, Löyttyniemi E, Myllyntausta S, Rautava P, Korhonen PE. Factors associated with quality of life and work ability among Finnish municipal employees: a cross-sectional study. *BMJ Open*. 2020;10(9):e035544.
32. Chu SY, Tsai YH, Xiao SH, Huang SJ, Yang CC. Quality of return to work in patients with mild traumatic brain injury: a prospective investigation of associations among post-concussion symptoms, neuropsychological functions, working status and stability. *Brain Inj*. 2017;31(12):1674-1682.
33. Dweck MR, Bularga A, Hahn RT, et al. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging*. 2020;21(9):949-958.
34. Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. *Clin Auton Res*. 2020;30(5):449-451.
35. Kanjwal K, Jamal S, Kichloo A, Grubb BP. New-onset postural orthostatic tachycardia syndrome following coronavirus disease 2019 infection. *J Innov Card Rhythm Manag*. 2020;11(11):4302-4304.
36. Leddy JJ, Baker JG, Willer B. Active rehabilitation of concussion and post-concussion syndrome. *Phys Med Rehabil Clin N Am*. 2016;27(2):437-454.
37. Leddy JJ, Wilber CG, Willer BS. Active recovery from concussion. *Curr Opin Neurol*. 2018;31(6):681-686.
38. Goodwin VA, Allan L, Bethel A, et al. Rehabilitation to enable recovery from COVID-19: a rapid systematic review. *Physiotherapy*. 2021;111:4-22.
39. Chu L, Valencia IJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: a patient-centered, cross-sectional survey. *PLoS One*. 2018;13(6):e0197811.
40. Sheehy LM. Considerations for postacute rehabilitation for survivors of COVID-19. *JMIR Public Health Surveill*. 2020;6(2):e19462.