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

VISHAL KHETPAL, MD; JULIA BERKOWITZ, MD; SHILPA VIJAYAKUMAR, MD; GAURAV CHOUDHARY, MBBS; JON A. MUKAND, MD, PhD; JAMES L. RUDOLPH, MD, SM; WEN-CHIH WU, MD, MPH; SEBHAT ERQOU, MD, PhD

ABSTRACT

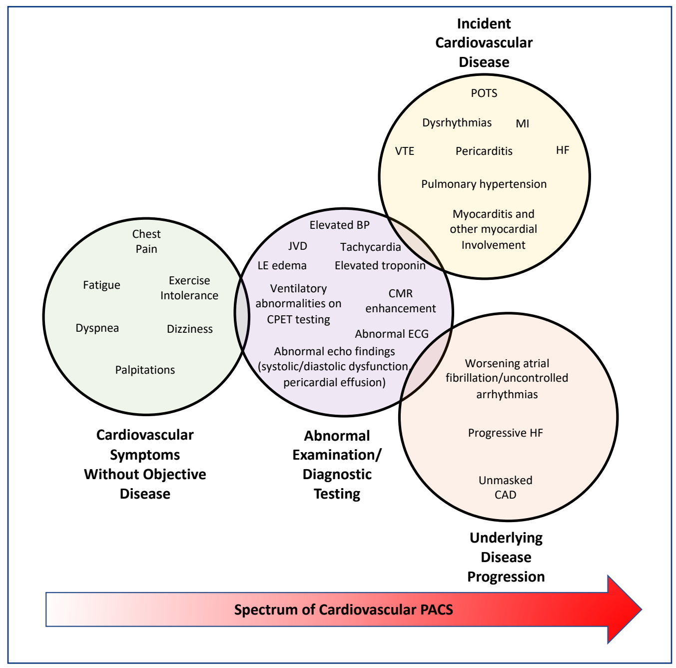
Survivors of coronavirus disease 2019 (COVID-19) may experience persistent symptoms, abnormal diagnostic test findings, incident disease in specific organ systems, or progression of existing disease. Post-acute COVID-19 syndrome (PACS) is defined by persistent, recurrent, or new symptoms, findings, or 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

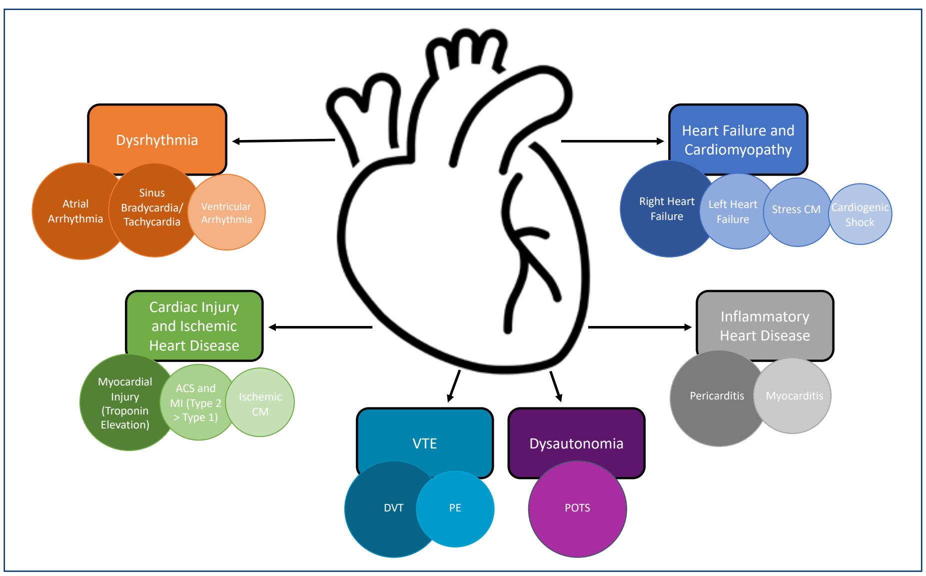
Beyond the first 30 days of illness, COVID-19 survivors, both those who required hospitalization and those with milder cases, have reported a broad range of cardiovascular symptoms, including dyspnea,[8,9] chest pain,[8-10] palpitations,[8-12] dizziness and tachycardia[13] (**Table 1**[14,15]). Ramadan 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]

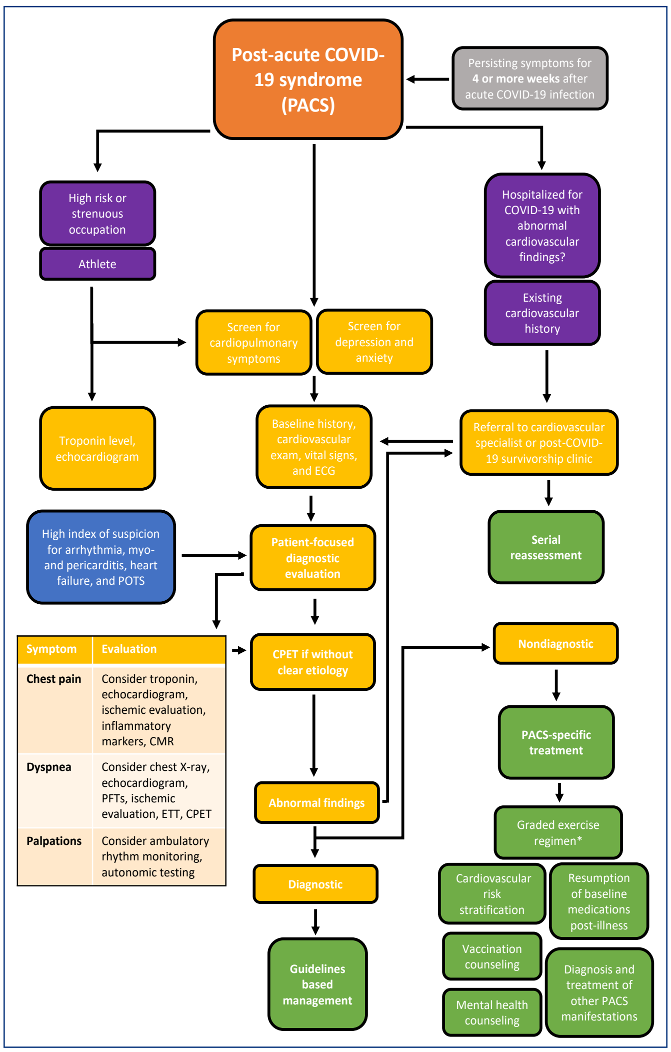
PACS, pulmonary hypertension, and right heart failure

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.

References

1. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med*. 2021;27(4):601-615. doi:10.1038/s41591-021-01283-z
2. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594(7862):259-264. doi:10.1038/s41586-021-03553-9
3. Tudoran C, Tudoran M, Cut TG, et al. Evolution of Echocardiographic Abnormalities Identified in Previously Healthy Individuals Recovering from COVID-19. *J Pers Med*. 2022;12(1):46. doi:10.3390/jpm12010046
4. Breitbart P, Koch A, Schmidt M, et al. Clinical and cardiac magnetic resonance findings in post-COVID patients referred for suspected myocarditis. *Clin Res Cardiol*. 2021;110(11):1832-1840. doi:10.1007/s00392-021-01929-5
5. Saricam E, Dursun AD, Sariyildiz GT, et al. Laboratory and Imaging Evaluation of Cardiac Involvement in Patients with Post-Acute COVID-19. *Int J Gen Med*. 2021;14:4977-4985. doi:10.2147/IJGM.S321153
6. Huang L, Zhao P, Tang D, et al. Cardiac Involvement in Patients Recovered From COVID-2019 Identified Using Magnetic Resonance Imaging. *JACC Cardiovasc Imaging*. 2020;13(11):2330-2339. doi:10.1016/j.jcmg.2020.05.004
7. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. Published online February 7, 2022:1-8. doi:10.1038/s41591-022-01689-3
8. Carvalho-Schneider C, Laurent E, Lemaignen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2021;27(2):258-263. doi:10.1016/j.cmi.2020.09.052
9. Ramadan MS, Bertolino L, Zampino R, Durante-Mangoni E, Monaldi Hospital Cardiovascular Infection Study Group. Cardiac sequelae after coronavirus disease 2019 recovery: a systematic review. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2021;27(9):1250-1261. doi:10.1016/j.cmi.2021.06.015

10. Carfì A, Bernabei R, Landi F, for the Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA*. 2020;324(6):603-605. doi:10.1001/jama.2020.12603
11. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *The Lancet*. 2021;397(10270):220-232. doi:10.1016/S0140-6736(20)32656-8
12. 1Romero-Duarte Á, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, et al. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med*. 2021;19(1):1-13.
13. Dixit NM, Churchill A, Nsair A, Hsu JJ. Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known? *Am Heart J Plus Cardiol Res Pract*. 2021;5:100025. doi:10.1016/j.ahjo.2021.100025
14. Gluckman TJ, Bhave NM, Allen LA, et al. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play. *J Am Coll Cardiol*. 2022;79(17):1717-1756. doi:10.1016/j.jacc.2022.02.003
15. Writing Committee Members, Bozkurt B, Das SR, et al. 2022 AHA/ACC Key Data Elements and Definitions for Cardiovascular and Noncardiovascular Complications of COVID-19: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. *J Am Coll Cardiol*. Published online June 22, 2022:S0735-1097(22)04579-X. doi:10.1016/j.jacc.2022.03.355
16. Coromilas EJ, Kochav S, Goldenthal I, et al. Worldwide survey of COVID-19–associated arrhythmias. *Circ Arrhythm Electrophysiol*. 2021;14(3):e009458.
17. Ingul CB, Grimsmo J, Mecinaj A, et al. Cardiac Dysfunction and Arrhythmias 3 Months After Hospitalization for COVID-19. *J Am Heart Assoc*. 2022;11(3):e023473. doi:10.1161/JAHA.121.023473
18. Musikantow DR, Turagam MK, Sartori S, et al. Atrial Fibrillation in Patients Hospitalized With COVID-19. *JACC Clin Electrophysiol*. 2021;7(9):1120-1130. doi:10.1016/j.jacep.2021.02.009
19. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022;28(3):583-590. doi:10.1038/s41591-022-01689-3
20. isco V, Vitale C, Rispoli A, et al. Post-COVID-19 Syndrome: Involvement and Interactions between Respiratory, Cardiovascular and Nervous Systems. *J Clin Med*. 2022;11(3). doi:10.3390/jcm11030524
21. Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J*. 2021;42(19):1866-1878.
22. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265-1273.
23. Martinez MW, Tucker AM, Bloom OJ, et al. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening. *JAMA Cardiol*. 2021;6(7):745-752.
24. Starekova J, Bluemke DA, Bradham WS, et al. Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging. *JAMA Cardiol*. 2021;6(8):945-950.
25. Fu H, Zhang N, Zheng Y, et al. Risk stratification of cardiac sequelae detected using cardiac magnetic resonance in late convalescence at the six-month follow-up of recovered COVID-19 patients. *J Infect*. 2021;83(1):119-145.
26. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol*. 2021;50:107300. doi:10.1016/j.carpath.2020.107300
27. Kunal S, Madan M, Tarke C, et al. Emerging spectrum of post-COVID-19 syndrome. *Postgrad Med J*. Published online December 8, 2021:postgradmedj-2020-139585. doi:10.1136/postgradmedj-2020-139585
28. Lee CCE, Ali K, Connell D, et al. COVID-19-Associated Cardiovascular Complications. *Dis Basel Switz*. 2021;9(3). doi:10.3390/diseases9030047
29. Martínez-Salazar B, Holwerda M, Stüdle C, et al. COVID-19 and the Vasculature: Current Aspects and Long-Term Consequences. *Front Cell Dev Biol*. 2022;10:824851. doi:10.3389/fcell.2022.824851
30. Cordeanu EM, Duthil N, Severac F, et al. Prognostic Value of Troponin Elevation in COVID-19 Hospitalized Patients. *J Clin Med*. 2020;9(12):4078. doi:10.3390/jcm9124078
31. Elseidy SA, Awad AK, Vorla M, et al. Cardiovascular complications in the Post-Acute COVID-19 syndrome (PACS). *Int J Cardiol Heart Vasc*. 2022;40:101012. doi:10.1016/j.ijcha.2022.101012
32. Ayoubkhani D, Khunti K, Nafilyan V, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *Bmj-Br Med J*. 2021;372:n693. doi:10.1136/bmj.n693
33. Szekely Y, Lichter Y, Taieb P, et al. Spectrum of Cardiac Manifestations in COVID-19. *Circulation*. 2020;142(4):342-353. doi:10.1161/CIRCULATIONAHA.120.047971
34. Giustino G, Croft LB, Stefanini GG, et al. Characterization of Myocardial Injury in Patients With COVID-19. *J Am Coll Cardiol*. 2020;76(18):2043-2055. doi:10.1016/j.jacc.2020.08.069
35. Shah RM, Shah M, Shah S, Li A, Jauhar S. Takotsubo Syndrome and COVID-19: Associations and Implications. *Curr Probl Cardiol*. 2021;46(3):100763. doi:10.1016/j.cpcardiol.2020.100763
36. Chatrath N, Kaza N, Pabari PA, et al. The effect of concomitant COVID-19 infection on outcomes in patients hospitalized with heart failure. *ESC Heart Fail*. 2020;7(6):4443-4447. doi:10.1002/ehf2.13059
37. Alvarez-Garcia J, Lee S, Gupta A, et al. Prognostic Impact of Prior Heart Failure in Patients Hospitalized With COVID-19. *J Am Coll Cardiol*. 2020;76(20):2334-2348. doi:10.1016/j.jacc.2020.09.549
38. Bisaccia G, Ricci F, Recce V, et al. Post-Acute Sequelae of COVID-19 and Cardiovascular Autonomic Dysfunction: What Do We Know? *J Cardiovasc Dev Dis*. 2021;8(11). doi:10.3390/jcdd8110156
39. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol Res*. 2021;69(2):205-211. doi:10.1007/s12026-021-09185-5
40. Patell R, Bogue T, Koshy A, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. *Blood*. 2020;136(11):1342-1346.
41. Pagnesi M, Baldetti L, Beneduce A, et al. Pulmonary hypertension and right ventricular involvement in hospitalised patients with COVID-19. *Heart*. 2020;106(17):1324-1331. doi:10.1136/heartjnl-2020-317355
42. Nuche J, Segura de la Cal T, Jiménez López Guarch C, et al. Effect of Coronavirus Disease 2019 in Pulmonary Circulation. The Particular Scenario of Precapillary Pulmonary Hypertension. *Diagnostics*. 2020;10(8):548. doi:10.3390/diagnostics10080548
43. Richter D, Guasti L, Koehler F, et al. Late phase of COVID-19 pandemic in General Cardiology. A position paper of the ESC Council for Cardiology Practice. *ESC Heart Fail*. Published online June 25, 2021. doi:10.1002/ehf2.13466
44. Dixit NM, Churchill A, Nsair A, Hsu JJ. Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known? *Am Heart J Plus Cardiol Res Pract*. 2021;5:100025. doi:10.1016/j.ahjo.2021.100025
45. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur Heart J*. 2022;43(11):1157-1172. doi:10.1093/eurheartj/ehac031
46. Vanichkachorn G, Newcomb R, Cowl CT, et al. Post–COVID-19 Syndrome (Long Haul Syndrome): Description of a Multidisciplinary Clinic at Mayo Clinic and Characteristics of the Initial Patient Cohort. *Mayo Clin Proc*. 2021;96(7):1782-1791. doi:10.1016/j.mayocp.2021.04.024

47. Zhang X, Wang F, Shen Y, et al. Symptoms and Health Outcomes Among Survivors of COVID-19 Infection 1 Year After Discharge From Hospitals in Wuhan, China. *JAMA Netw Open*. 2021;4(9):e2127403. doi:10.1001/jamanetworkopen.2021.27403
48. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-895.e20. doi:10.1016/j.cell.2022.01.014
49. Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. *Heart Rhythm*. 2021;18(4):508-509. doi:10.1016/j.hrthm.2020.12.007
50. Gaffney AW. The Long COVID Conundrum. *Am J Med*. 2022;135(1):5-6. doi:10.1016/j.amjmed.2021.07.037
51. Mancini DM, Brunjes DL, Lala A, Trivieri MG, Contreras JP, Natelson BH. Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post–Coronavirus Disease. *JACC Heart Fail*. 2021;9(12):927-937. doi:10.1016/j.jchf.2021.10.002
52. Sarfraz Z, Sarfraz A, Barrios A, et al. Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care. *J Prim Care Community Health*. 2021;12:21501327211023730. doi:10.1177/21501327211023726
53. Szlejf C, Suemoto CK, Santos IS, et al. Poorer cardiovascular health is associated with psychiatric comorbidity: results from the ELSA-Brasil Study. *Int J Cardiol*. 2019;274:358-365. doi:10.1016/j.ijcard.2018.06.037
54. Antonelli M, Penfold RS, Merino J, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis*. 2022;22(1):43-55. doi:10.1016/S1473-3099(21)00460-6
55. Besnier F, Bérubé B, Malo J, et al. Cardiopulmonary Rehabilitation in Long-COVID-19 Patients with Persistent Breathlessness and Fatigue: The COVID-Rehab Study. *Int J Environ Res Public Health*. 2022;19(7):4133. doi:10.3390/ijerph19074133
56. Shechter A, Yelin D, Hamdan A, et al. Cardio-COVID clinic – a one-center experience. *Eur Heart J*. 2021;42(Supplement_1):ehab724.2738. doi:10.1093/eurheartj/ehab724.2738
57. Erqou S, Zullo AR, Jiang L, et al. Specifying uniform eligibility criteria to strengthen causal inference studies of long-term outcomes of COVID-19. Published online May 30, 2022:2022.05.30.22275733. doi:10.1101/2022.05.30.22275733

Authors

Vishal Khetpal, MD, Department of Medicine, Brown University, Providence, RI.

Julia Berkowitz, MD, Department of Medicine, Brown University, Providence, RI.

Shilpa Vijayakumar, MD, Department of Medicine, Brown University, Providence, RI.

Gaurav Choudhary, MBBS, Department of Medicine, Brown University, Providence, RI; Department of Medicine, Providence VA Medical Center, Providence, RI.

Jon A. Mukand, MD, PhD, Rehab Medicine Life Care Plans; Clinical Assistant Professor of Orthopaedics, Alpert Medical School of Brown University, Providence, RI.

James L. Rudolph, MD, SM, Department of Medicine, Brown University, Providence, RI; Department of Medicine, Providence VA Medical Center, Providence, RI; Innovation in Long Term Services and Supports, Providence VA Medical Center, Providence, RI; School of Public Health, Brown University, Providence, RI.

Wen-Chih Wu, MD, MPH, Department of Medicine, Brown University, Providence, RI; Department of Medicine, Providence VA Medical Center, Providence, RI; Innovation in Long Term Services and Supports, Providence VA Medical Center, Providence, RI; School of Public Health, Brown University, Providence, RI.

Sebhat Erqou, MD, PhD, Department of Medicine, Brown University, Providence, RI; Department of Medicine, Providence VA Medical Center, Providence, RI; Innovation in Long Term Services and Supports, Providence VA Medical Center, Providence, RI.

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.

Correspondence

Sebhat Erqou, MD
Providence VA Medical Center, Division of Cardiology
830 Chalkstone Avenue
Providence, RI
401-273-7100
Fax 401-457-3357
sebhat.erqou@va.gov; Sebhat_erqou@brown.edu