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Review Article

Post-Acute COVID-19 Syndrome and the cardiovascular system: What is known?

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ABSTRACT

Post-Acute COVID-19 Syndrome (PACS) is defined by persistent symptoms >3–4 weeks after onset of COVID-19. The mechanism of these persistent symptoms is distinct from acute COVID-19 although not completely understood despite the high incidence of PACS. Cardiovascular symptoms such as chest pain and palpitations commonly occur in PACS, but the underlying cause of symptoms is infrequently known. While autopsy studies have shown that the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) rarely causes direct myocardial injury, several syndromes such as myocarditis, pericarditis, and Postural Orthostatic Tachycardia Syndrome have been implicated in PACS. Additionally, patients hospitalized with acute COVID-19 who display biomarker evidence of myocardial injury may have underlying coronary artery disease revealed by the physiological stress of SARS-CoV-2 infection and may benefit from medical optimization. We review what is known about PACS and the cardiovascular system and propose a framework for evaluation and management of related symptoms.

1. Introduction

For those suffering from what has become known as "Long COVID," "Chronic COVID Syndrome," "Long-Haul COVID," "Post-Acute Sequelae of SARS-CoV-2 infection," and "Post-Acute COVID-19 Syndrome (PACS)," scientific understanding of the phenomenon has been painfully slow [1]. Most often defined as persistent symptoms >3–4 weeks from the initial onset of COVID-19 symptoms, PACS (we will use this term hereafter) is characterized by a combination of non-specific symptoms, most commonly: fatigue, dyspnea, cough, and continued loss of smell [2–4]. Cardiovascular symptoms such as palpitations and chest pain in PACS can be a clinical dilemma. Clinicians may be unsure if these symptoms are part of the non-specific PACS milieu or represent pathology in the cardiovascular system. We review what is known about PACS and the cardiovascular system and propose a framework for evaluation and management of such symptoms.

2. Methods

A review of literature on the effect of PACS on the cardiovascular system was conducted using a Medline (PubMed) database search. Cohort studies of long-term outcomes of patients following recovery from COVID-19 were identified and compiled; the results of which are summarized in Table 1. Literature pertaining to specific cardiovascular syndromes implicated in PACS was individually searched with separate inclusion and exclusion criteria. Details of search strategy, inclusion and exclusion criteria, and search results can be found in Supplementary File 1.

Abbreviations: ACE2, angiotensin converting enzyme-2; AF/AFL, atrial fibrillation or flutter; CMR, cardiac magnetic resonance imaging; CV, cardiovascular; CFS, Chronic Fatigue Syndrome; CBT, cognitive behavioral therapy; CRP, C-reactive protein; ECG, electrocardiography; ECV, extracellular volume; LGE, late gadolinium enhancement; MCAS, Mast Cell Activation Syndrome; MERS, Middle East Respiratory Syndrome; POTS, Post-Acute COVID-19 Syndrome; SARS-COV-1, Severe Acute Respiratory Syndrome Coronavirus-1; TTT, tilt table testing; T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction.

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3. Acute COVID-19 and the cardiovascular system

Early in the pandemic, COVID-19 was theorized to have the potential to injure the heart through an angiotensin converting enzyme-2 (ACE2) receptor mediated process [5,6]. Elevations in troponin, which occurred in roughly 20–30% of hospitalized patients [7,8], strongly correlated with mortality, increasing odds of death by 2–5 times depending on the degree of elevation [7]. As our understanding developed, the etiology of

Table 1
Longitudinal studies of Post-Acute COVID-19 Syndrome.

First author	Patients	Mean follow up time	Population	General symptoms	CV symptoms	Notes
Chopra [83]	488	~60 days	Hospitalized	Persistent symptoms of illness, 32.5%; DOE, 22.9%	"Chest problem" on exertion, 16.6%	15.1% readmitted 24.1% with CV disease
Huang [17]	1733	186 days	Hospitalized	Fatigue and muscle weakness, 63%; 6MWT below age predicted normal, ~25%	Palpitations, 9%; dizziness, 6%; chest pain, 5%	7% with CV disease
Mandal [16]	384	54 days	Hospitalized	Fatigue, 67.3–76.9%[a]; Breathlessness, 54.8–63.3%[a]	Not reported	9.7% with CV disease
Petersen [18]	98	125 days	96% non-hospitalized	Fatigue, 29%; loss of smell/taste, 23%; dyspnea, 9%	Chest tightness, 5%	No differences found between those with hypertension, hypercholesterolemia, or diabetes
Carfi [84]	143	60 days	Hospitalized	Fatigue 53.1%; dyspnea 43.4%	Chest pain, 21.7%	35% with hypertension; 7% with diabetes; 4.9% with CV disease
Xiong [85]	538	97 days	Hospitalized	Fatigue, 28.3%	Dizziness, 2.6%; chest pain, 12.3%; "CV related symptoms," 13%; resting HR increase, 11.2%	All symptoms were significantly more common compared to risk factor matched controls
Kamal [86]	287	>20 days	80.2% mild severity of disease	Fatigue, 72.8%; dyspnea, 28.2%	Chest pain, 28.9%	Self-reported: Myocarditis, 1.4%; arrhythmia, 0.3%
Carvalho-Schneider [87]	150	60 days	65% non-hospitalized	At day 60: respiratory symptoms, 91%; flu-like symptoms, 87%; dyspnea, 45%	Chest pain, 16%	49% with no comorbid conditions; 34% drop out rate
Garrigues [88]	120	110 days	Hospitalized	Fatigue, 55%; dyspnea, 42%; cough, 25%	Did not resume sports, 28%; chest pain, 11%	47% with hypertension; 22% with diabetes
Halpin [89]	100	48 days	Hospitalized	Fatigue, 64%; breathlessness, 50%; difficulty with usual activities, 44%	Not reported	10% with CAD, 5% with HF, 41% with hypertension
Moreno-Perez [90]	277	77 days	66% Hospitalized	Dyspnea, 34.4%; abnormal spirometry, 9%	Not reported	36.5% with hypertension, 11.6% with diabetes, 6.9% with CV disease
Logue [19]	177	169 days	91% with mild or asymptomatic COVID-19	Fatigue, 13.6%; shortness of breath, ~5%; myalgia ~5%	Not reported	13.0% with hypertension, 5.1% with diabetes
Morin [91]	478	113 days	All hospitalized, 30% in ICU	Fatigue, 31.1%; dyspnea, 16.3%	Chest pain 8.1%	25.3% with RV dilation, 12.0% with LVEF $\leq$ 50% (all ICU, no baseline reported), 19.4% with fibrotic lung lesions
Havervall [20]	323	8 months	Healthcare workers without severe COVID-19	Fatigue, 4.0%; dyspnea, 1.9%	Palpitations, 0.6%	Average age 43 years, 83% were women, 0.7% reported palpitations in COVID-19 negative control
Shang [92]	1174	6 months	All hospitalized	Fatigue, 25.3%; dyspnea, 20.4%; myalgia, 13.8%	Chest pain, 9.9%;	No difference in rate of symptoms found between age < 65 and age > 65, 52.1% with abnormal CT chest
Meije [93]	294	7 months	All hospitalized	Fatigue, 26.5%; myalgia, 13.3%; dyspnea, 9.5%	Chest pain, 2.7%	Patients with severe hypoxia had worse respiratory status at 7 months but similar incidence of other symptoms
Armange [94]	214	6 weeks	All non-hospitalized	Dyspnea, 40.2%; cough 19.2%	Chest pain, 10.7%	Only 55% of patients were able to resume sports at 6 weeks
Darley [95]	65	69 Days	86% non-hospitalized	Fatigue, 26.2%; dyspnea, 23.1%	Chest pain, ~5%	Average age 47 years
Jacobson [96]	118	3–4 months	81.4% non-hospitalized	Fatigue, 30.8%; dyspnea, 26.5%; myalgias, 17.9%	Chest pain, 13.7%; palpitations, 6.0%	Symptom burden did not differ between hospitalized and non-hospitalized patients except dyspnea was more common in hospitalized patients
de Graaf [97]	81	6 weeks	All hospitalized, 41% admitted to ICU	Dyspnea, 62%	Any chest pain, 14%; anginal chest pain, 1%; atypical chest pain, 4%; palpitations, 15%	Mean troponin 11 ng/L, mean NT-ProBNP 190 ng/L
Venturelli [98]	767	68 days	88.4% hospitalized, 8.6% admitted to ICU	Fatigue, 36.5%; dyspnea 32.7%; myalgia 5.7%	Chest pain, 4.7%; palpitations, 5.9%	8.2% received cardiology consultation in ambulatory setting
Liang [99]	76	3 months	Hospitalized	Fatigue, 59%; dyspnea, 61%	Chest pain, 62%; palpitations, 62%	86% healthcare worker

Abbreviations: 6MWT, 6-minute walk time; CT, computed tomography; CV, cardiovascular; DOE, dyspnea on exertion; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NT-ProBNP, n-terminal-pro brain natriuretic peptide; RV, right ventricle.

[a] Depending on level of care.

myocardial injury has shown to be mostly type 2 myocardial infarction (T2MI) in the setting of increased demand due to systemic inflammation [9,10]. Acute coronary syndrome and myocarditis are less commonly identified as causes for myocardial injury.

Based on autopsy studies, myocarditis in acute COVID-19 is relatively rare, present in <4.5% of autopsy cases [11] and has a lymphocytic predominance [12]. Viral inclusions are rarely seen, suggesting myocarditis in acute COVID-19 is a sequela of an inflammatory response rather than direct viral attack.

Thrombotic events are also common in hospitalized patients with pulmonary embolism, deep vein thrombosis, and stroke seen in 3.2%, 3.9%, and 1.6% of patients hospitalized with COVID-19, respectively [13]. Thrombosis is likely due to the inflammatory state induced by COVID-19 [14]. Right ventricular dilation is commonly seen in severe COVID-19 as a downstream consequence of acute pulmonary disease [15].

3.1. What is PACS?

In contrast to acute COVID-19, PACS is defined by the persistence of COVID-19 symptoms for >3–4 weeks [4]. The pathophysiological mechanisms for PACS are not well defined but appear to be different from acute COVID-19. In a follow-up study of 384 patients hospitalized for COVID-19, elevations of D-dimer, ferritin, and C-reactive protein (CRP) normalized within 2 months following discharge [16]. Chest radiographs remained abnormal or worsened in just over 10% of patients. However, in contrast to improving laboratory and imaging findings, fatigue and breathlessness were present in nearly two-thirds of patients.

The course of PACS tends to be significantly prolonged. Huang et al. found 76% of patients had at least 1 persistent symptom of COVID-19 at a mean of 186 days from hospital discharge [17]. Generalized deconditioning was most common with 63% reporting fatigue and muscle weakness. One-quarter had 6-minute walk times below the age-predicted lower limit of normal months after hospitalization.

These findings of persistent symptoms are not limited to hospitalized patients. In a cohort of 98 non-hospitalized patients, fatigue was present in 29%, loss of smell and/or taste in 23%, and dyspnea in 9% several months after their initial COVID-19 illness [18]. Other studies in cohorts of asymptomatic or mild COVID-19 report lower incidences of PACS, but persistent symptoms as far as 8 months are still reported in over 10% of these patients [19–20]. No studies have demonstrated that PACS exhibits a predisposition to any gender, age, race, or preexisting condition, although PACS is more common in those with severe COVID-19. Table 1 summarizes published studies of persistent symptoms following COVID-19.

4. Cardiovascular manifestations of PACS

The most common cardiovascular (CV) symptoms present in PACS are chest pain or tightness, palpitations, dizziness, and an increase in resting heart rate (Table 1). These symptoms appear in both hospitalized and non-hospitalized groups. There is no clear relationship with CV symptoms and preexisting CV disease in PACS.

The underlying pathophysiological link between PACS and the CV system has not definitively been established, but several CV syndromes may be implicated. The evidence for each is summarized in the following sections.

4.1. Myocarditis

Concern for myocarditis in the post-acute COVID-19 period became heightened with the publication of several studies in mid-2020 that suggested an alarmingly high prevalence of imaging abnormalities suggestive of myocardial injury and inflammation.

In a study of 29 patients previously hospitalized with COVID-19 and elevated troponin of unknown cause, 45% had late gadolinium enhancement (LGE) in a non-ischemic, “myocarditis-like” pattern on cardiac magnetic resonance imaging (CMR) approximately 27 days after discharge [21]. Notably, these patients did not have increased CRP or troponin levels, and all had normal left ventricular ejection fraction (LVEF) without wall motion abnormalities, although additional parameters such as myocardial strain were not reported. In a study of Ohio State University athletes, 15% had findings on CMR that met the updated Lake Louise main criteria for the imaging diagnosis of myocarditis which are: 1) myocardial edema by T2-mapping or T2-weighted images, and 2) non-ischemic myocardial injury by abnormal T1 signal, extracellular volume (ECV) or LGE [22,23]. While the study drew significant media attention, it was limited by a lack of a control cohort and a study population with no symptoms of myocarditis. Huang et al. studied 26 patients recovered from COVID-19 (mean 47 days) with at least 1 persistent cardiovascular symptom (e.g., chest pain, palpitations, chest distress) and found that 58% had abnormalities on CMR [24]. While elevations in T1, T2, ECV and LGE were reported, the updated Lake Louise criteria were not used. Additionally, the percentage of abnormalities in the control group was not reported. No difference in troponin, BNP, and CRP were noted between patients with normal and abnormal CMRs. Notably, some patients with normal CMRs were symptomatic as well.

Puntmann et al. performed CMR on both hospitalized and non-hospitalized patients at least 2 weeks after diagnosis with COVID-19 and purposely excluded those with cardiac symptoms [25]. They still found significantly abnormal T2 signal and non-ischemic LGE in 22% and 20% of patients, respectively, compared to 0% and 7% in risk factor-matched controls. A multicenter study evaluated 148 discharged patients with prior hospitalization and troponin elevation a median 68 days from discharge [26]. Myocarditis-like scar was found in 26% but injury was limited to three or fewer myocardial segments in 88% of patients, and all had normal LVEF without wall motion abnormalities. Active myocarditis, defined by regional elevation in T1 and T2 signal (or T2 signal alone) in the same distribution as LGE, was found in 8% of patients. Elevated troponin during hospitalization was not predictive of non-ischemic pattern LGE or signal of active myocarditis.

Recently, Fu et al. reported on the results of CMR on patients 4–6 months post-hospitalization for COVID-19. Compared to healthy controls, COVID-19 survivors were more likely to show myocardial edema (29%) and fibrosis (4%); however, none of the patients reported cardiovascular-related symptoms during follow up [27].

In contrast to the high rates of myocardial edema and LGE suggestive of active or resolved myocarditis found in the aforementioned studies in mostly hospitalized older patients, more recent studies reported far lower incidences of myocarditis in athletes. Clark et al. reported on 59 athletes with prior COVID-19 and found only 2 patients who met the updated Lake Louise criteria for myocarditis (myocardial edema and non-ischemic myocardial injury on CMR) [28]. This patient had no abnormality in electrocardiography (ECG), cardiac biomarkers, or systolic function. Starekova et al. reported on 145 student athletes a median 15 days after a positive test and found only 2 patients (1.4%) that met Lake Louise criteria for myocarditis [29]. One patient had dyspnea, mild troponin elevation, and non-specific ST changes on ECG; the other had “mild-moderate” symptoms without any other abnormalities. In the spring of 2020, several major American sports leagues partnered with clinical investigators to systematically screen COVID-19 positive athletes for myocarditis before return-to-play. All COVID-19 positive athletes were screened with a serum troponin measurement, ECG, and resting echocardiogram. Those with concerning findings were further screened with CMR and/or stress echocardiogram. Out of 789 athletes (0 with severe COVID-19), 27 had abnormalities on initial screening necessitating CMR, of which 3 had imaging findings consistent with active myocarditis and 2 with active pericarditis.

Moulson et al. reported the results of a large multicenter prospective cohort study of 19,378 college age athletes who underwent systematic screening for cardiac abnormalities after recovery from COVID-19 [30].

Seventeen percent of athletes tested positive for SARS-CoV-2 and most underwent "triad testing" with ECG, troponin, TTE, followed by CMR if indicated. Only 3.0% of the 198 patients who were screened with CMR had a "definitive, probable or possible" pathology attributable to COVID-19. However, in the authors subsequent analysis, the presence of cardiopulmonary symptoms during acute infection or on resumption of exercise or abnormal testing on any "triad test" increased odds of an abnormality on CMR by factor of 4.2 and 48.2, respectively. The authors concluded that a stepwise approach that used the presence of moderate/severe symptoms, cardiopulmonary symptoms or any abnormal "triad test" to trigger screening with CMR would have identified 82% of the athletes with "definite or probable" myocardial or pericardial involvement.

In a non-athlete population, a prospective study of 149 healthcare workers, showed no differences in CMR characteristics, troponin level, and N-terminal pro-BNP at 6 months post-infection versus age, sex, and ethnicity matched seronegative controls [31]. The study patient population had relatively few comorbidities and only 1 patient had severe COVID-19.

Although most of the studies used blinded review by multiple independent radiologists, methodologies of many of the earlier studies, such as the lack of comparable control groups or use of updated Lake Louise criteria, raise the question of whether the incidence of myocarditis was vastly overestimated. The results of more recent, larger scale studies suggest myocarditis is relatively rare and is unlikely to contribute to a significant percentage of PACS cases even those with predominant CV symptoms, especially in cases of asymptomatic or mild COVID-19. Additionally, myocardial edema, which is relatively common in patients recovered from severe COVID-19, appears to be of limited clinical consequence, especially in the absence of other objective evidence of pathology, such as systolic dysfunction, elevations in cardiac biomarkers, or ECG abnormalities. Similarly, persistent LGE, which has been shown in non-COVID-19 cohorts to be a prognosticator of cardiac events such as cardiac arrest, implantable cardiac defibrillator shock, heart transplantation, and heart failure hospitalization, has not been shown to be associated with these events in COVID-19 cohorts [32]. Further study is needed to determine the highest value screening protocol for myocarditis in patients with varying degree of COVID-19 severity, but a stepwise approach to screening based on symptoms with initial testing using cost-effective cardiodiagnostics is likely prudent.

4.2. Postural Orthostatic Tachycardia Syndrome

Postural Orthostatic Tachycardia Syndrome (POTS) is defined as an inappropriate rise in heart rate without change in blood pressure upon movement from a recumbent to an upright position [33]. POTS has previously been implicated in persistent post-viral symptomatology, with over 40% of POTS cases thought to be associated with viral infection, possibly triggered by induced autoimmunity or molecular mimicry. POTS has been suggested as a possible etiology for symptoms of chest pain, palpitations, and dizziness in patients with PACS [34].

In one report, a previously healthy 36-year-old woman presented with persistent palpitations and chest pain following mild COVID-19 infection [35]. In-office orthostatic vital sign measurement and tilt table testing (TTT) confirmed a diagnosis of POTS. In two other reports, patients presented with fatigue, dizziness, and palpitations and had a diagnosis of POTS subsequently confirmed by autonomic testing [36,37]. A Swedish case series described 3 patients with highly symptomatic POTS after COVID-19 [38]. All 3 patients had persistent symptoms of increased heart rate upon standing, palpitations, and fatigue. Despite multiple treatment modalities, they remained highly symptomatic.

In a larger case series of 28 patients presenting (self- or practitioner-referred) to a Dysautonomia Clinic with persistent neurologic and cardiovascular complaints after COVID-19, 20 patients had evidence of new orthostatic intolerance defined by TTT or 10-minute stand test [39]. The majority (70%) were women, none had been hospitalized, and 80% required pharmacological treatment. Fifteen patients met the diagnostic criteria for POTS; the others were diagnosed with neurocardiogenic syncope and orthostatic hypotension.

In two other case series with a total of 10 patients diagnosed with POTS, the timing of POTS symptom onset was most often concurrent with usual acute COVID-19 symptoms but cases of POTS occurring up to months after initial infection were seen [40,41]. In both series autonomic symptoms usually persisted several months after the resolution of acute infection.

To date, no studies have formally evaluated a cohort of patients with PACS for POTS, which may be due to provider unfamiliarity with the syndrome [42]. In an online survey of those with persistent symptoms of COVID-19, 54% reported an increase in resting heart rate [43]. Whether this could be related to POTS is unclear, and further research is needed to determine if patients with the constellation of tachycardia, palpitations, and dizziness after COVID-19 may be suffering from POTS. Treatment of POTS varies by degree of symptoms and typically includes a combination of physical and behavioral exercises and sometimes medication [33].

4.3. Arrhythmia

Arrhythmia has been associated with acute COVID-19, especially in critically ill patients and those treated with arrhythmogenic and QT prolonging meds such as hydroxychloroquine and azithromycin [44]. In a study of 50 consecutive admitted patients, ECG changes and arrhythmias were varied (e.g., atrial fibrillation, premature ventricular complexes, heart block), but overall, most patients had ECGs similar to their baseline hospital admission ECGs [45]. When changes did occur, patients were typically 20–30 days into their hospitalization, suggesting a correlation with sicker patients. Musikantow et al. retrospectively studied the incidence of atrial fibrillation or flutter (AF/AFL) in over 5000 hospitalized patients with COVID-19 or influenza, finding similar rates of AF/AFL in both groups with an association between arrhythmia and elevations in inflammatory markers, myocardial injury, and death [46]. The results suggest AF/AFL during COVID-19 hospitalization occurs as a consequence of severe systemic disease. Follow-up study on whether AF/AFL remained persistent is lacking.

A link between COVID-19 and arrhythmias post-hospitalization or in those who never required hospitalization is less clear. In the studies reporting myocarditis mentioned earlier, no arrhythmias were reported. A review of the Veterans Health Administration electronic medical record showed a 1.7 times higher incidence of arrhythmia at 6-months post-COVID-19 in non-hospitalized patients compared to matched controls; however, whether this was due to truly higher arrhythmia burden or higher rate of detection in the COVID-19 cohort is unknown [47]. To date, ambulatory monitoring of COVID-19 patients in the post-acute phase has yet to be reported. Wearable devices may be able to provide such information [48].

4.4. Pericarditis

Most cases of pericarditis in the general population are idiopathic but the prevailing opinion is that these cases may be sequelae of viral infections [49]. In hospitalized patients with COVID-19, diffuse acute ST changes consistent with pericarditis were present in 12% in one study [45]. In an imaging study of 59 collegiate athletes, Clark et al. found just one case of pericarditis [28]. Pericarditis was present in just 0.3% of competitive athletes systematically screened after COVID-19 [50]. Puntmann et al. reported that 20% of patients had a pericardial effusion >1 cm on CMR versus 7% in risk factor-matched controls, though no patients had symptoms [25]. Kotecha et al. and Moulson et al. each reported a 5% incidence of pericardial effusion, mostly small in size [26,30]. Overall, it appears small pericardial effusions may be relatively

common in the post-acute period of COVID-19, but pericarditis, especially with symptoms, is rarer.

4.5. Unmasked coronary artery disease

As previously mentioned, 20–30% of patients hospitalized with COVID-19 will have elevations in troponin levels, most often as a result of T2MI [7,8]. T2MI should not be ignored following resolution of acute illness. In a study of 2122 patients (non-COVID-19) with a troponin I peak >0.05 ng/L during hospitalization, 5 year all-cause mortality was 62.5% in those with T2MI compared to 36.7% in those with a type 1 myocardial infarction (T1MI) [51]. Although death from comorbid conditions was more common in the T2MI group, death from CV cause was equal in the two groups. Other studies have shown that ~50% of those who have a T2MI have underlying CAD [52]. However, these lesions are unlikely to show coronary obstruction >50% on angiography.

In patients hospitalized with COVID-19, troponin >99th percentile was associated with a 3–6 times greater likelihood of a history of CAD [53–55]. A preliminary report by Nai Fovino et al. showed a trend toward higher high-sensitivity troponin peak during COVID-19 hospitalization in patients with a coronary artery calcium score > 400 versus those with a score < 400 (1424 versus 419 ng/L, $p = .084$) [56].

Interestingly, patients with COVID-19 were shown to have a 3 times higher likelihood of a major adverse cardiac event assessed at a median of 5 months post-discharge compared to age, sex, and risk factor matched controls [57]. The etiology of this association requires further study.

In short, evaluation of patients who experienced T2MI during a COVID-19 hospitalization could identify individuals with subclinical CAD in need of medical optimization. Additionally, those with preexisting risk factors for CV events may require closer monitoring following COVID-19.

5. What can be learned from other viral syndromes?

Madjid et al. previously described a weak association between acute Severe Acute Respiratory Syndrome Coronavirus-1 (SARS-CoV-1) and acute Middle East Respiratory Syndrome (MERS) and cardiovascular complications such as T1MI, arrhythmia, and transient diastolic dysfunction [58]. A review of 28 studies categorized the long-term symptoms of the SARS-CoV-1 and MERS viruses many of which, such as fatigue, dyspnea, and weakness, were similar to PACS. Additionally, peak oxygen uptake was impaired in 41% of patients at 3 months. Another study of 22 patients with SARS-CoV-1 with persistent symptoms (mean 19.8 months) again found symptoms similar to PACS: fatigue, myalgias, weakness, depression, and abnormal sleep studies [59]. Given the relatively low case counts in the SARS-CoV-1 and MERS epidemics, robust conclusions of post-infectious CV symptoms are unable to be drawn.

Looking beyond the coronavirus family, many viral infections are associated with Chronic Fatigue Syndrome (CFS) following recovery [60]. CFS is defined as severe, disabling post-exertional fatigue that affects physical and mental functioning. Fever, headache, sore throat, cough, myalgia, and fatigue are the predominant symptoms but differ from patient to patient [61]. Symptoms must occur at least 50% of the time for a minimum of 6 months [60]. Cognitive behavioral therapy (CBT) with graduated physical exercise can be an effective treatment in CFS [61]. Pharmacologic treatment with anti-depressants, steroids, and vitamin supplements has shown mixed results in small-scale clinical trials [62]. Given that the symptoms of PACS bear a strong resemblance to CFS, CBT with graduated exercise should be explored in future studies as a possible treatment modality in PACS.

5.1. Mast Cell Activation Syndrome

Mast Cell Activation Syndrome (MCAS) is a multisystem, inflammatory disease caused by mast cell hyperactivity and release of inflammatory cytokines [63]. Symptoms experienced in MCAS largely overlap with those seen in PACS, including chest pain, palpitations, and dyspnea. Some have theorized that prolonged COVID-19 symptomatology may be due to abnormal hyperactivation of mast cells in patients with underlying primary MCAS [64]. Mast cells express a number of surface proteins to recognize pathogens; however, they also express ACE2 making them susceptible to the direct attack from SARS-CoV-2. However, this potential mechanism remains theoretical since to date experimental studies linking MCAS and PACS are lacking.

5.2. Deconditioning

Deconditioning during acute illness has previously been shown to have lasting effects on individuals after recovery [65]. Even young, healthy patients may experience rapid physiologic change after a relatively brief period of inactivity. A study of 7 healthy young males showed a 12.3% decrease in VO_2 max after just 2 weeks of bed rest [66]. Mild-to-moderate acute COVID-19 has been shown to have symptoms lasting an average of 6–17 days, potentially leading to significant deconditioning [67]. Some authors have suggested symptomatic and physiological changes that may occur after periods of deconditioning parallel those of POTS and CFS [68]. Graduated exercise is the only effective treatment for deconditioning [65].

6. How can we manage cardiovascular manifestations of PACS?

The true risk of an underlying cardiovascular pathology for those with PACS is difficult to assess. While more cases of myocarditis, POTS, and pericarditis will undoubtedly be identified, indiscriminate testing will incur a substantial burden on the healthcare system. On the other hand, future studies are needed to prospectively follow and thoroughly evaluate those with PACS to determine the most appropriate workup. Basic science research is needed to identify the underlying pathophysiology of PACS and any links to similar syndromes such as MCAS and CFS.

CMR techniques and reporting need to be more standardized to detect true myocarditis and these findings need to be correlated with symptoms and objective findings on ECG, ambulatory cardiac

Table 2
Priority areas for further study of cardiovascular involvement in Post-Acute COVID-19 Syndrome.

Syndrome	Area of need	Potential impact
Myocarditis/ pericarditis	Long term significance of myocardial edema, LGE, and pericardial abnormalities seen in patients recovered from severe COVID-19	Understanding of incidental CMR findings, long-term functional consequence, and natural history Reduction in unnecessary diagnostic testing
POTS	Prevalence of patients with POTS following COVID-19	Aggregation of large cohorts of patients to trial potential treatments
Arrhythmia	Ambulatory cardiac monitoring following hospitalization with COVID-19 or in patients with persistent palpitations	Determination of the frequency of long-term arrhythmia in patients recovered from COVID-19
CFS, MCAS, and deconditioning	Link and overlap of these syndromes with PACS	Identification of a plausible biological mechanism for PACS symptoms
"Unmasked" coronary artery disease	Long-term outcomes of patients with troponin elevations during hospitalization for COVID-19	Identification of a population with sub-clinical CAD that will benefit from medical optimization

Abbreviations: CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CFS, Chronic Fatigue Syndrome; LGE, late gadolinium enhancement; MCAS, Mast Cell Activation Syndrome; PACS, Post-Acute COVID-19 Syndrome; POTS, Postural Orthostatic Tachycardia Syndrome.

monitoring, and echocardiogram. Table 2 summarizes priority areas for additional study.

For athletes, return to competitive sports after PACS will require more scrutiny. Multiple authors and societies have proposed return-to-play guidelines following COVID-19 infection [69–73]. Early recommendations proposed more conservative return-to-play timelines due to concern for a high incidence of myocarditis after COVID-19. However, subsequent research has shown a lower incidence of myocarditis in populations of relatively younger athletes, especially in those with minimal symptoms. Additionally, few cases of sudden cardiac arrest, the feared complication of myocarditis, have been reported [74].

A reasonable approach to return-to-play after COVID-19 is graded resumption of activity and exercise [69–73]. Additional testing can be considered for those with elevated troponin during hospitalization, new or persistent CV symptoms, or CV risk factors seeking to return to a high level of physical activity. Exercise restriction is reasonable in patients with persistent symptoms of palpitations or chest pain prior to exclusion of myocarditis or pericarditis. If myocarditis or pericarditis is diagnosed, patients should be counseled on return-to-play guidelines such as those found in the 2019 Position Statement from the Sports Cardiology Section of the European Association of Preventive Cardiology [75].

Many centers have established COVID-19 ambulatory clinics [76]. A few, including our own, have created COVID-19 cardiology clinics [77–79]. Such clinics will develop expertise that will lead to more focused and cost-effective evaluation of those with CV symptoms of PACS. Multidisciplinary PACS clinics may provide a comprehensive evaluation of symptoms that often reach across disciplines, including pulmonology, cardiology, neurology, rheumatology, and psychiatry [4,76]. Fig. 1 displays our approach for evaluation of recovered patients with CV symptoms following COVID-19 or a prior COVID-19 hospitalization with cardiac complications based upon the available evidence reviewed above.

7. Conclusion

With the emerging success of the COVID-19 vaccines, the burden of acute COVID-19 will wane, but we will likely be left with a significant number of patients with persistent symptoms even months after COVID-19 infection [80,81]. PACS has become a top priority for the healthcare system, and federal institutions such as the National Institutes of Health have dedicated significant funding for research into this new, likely chronic disease process [82]. As the medical community gains a deeper understanding of PACS and its cardiovascular manifestations over the coming years, we will hopefully enhance our ability to identify those at increased risk of these complications and discover effective strategies to prevent and treat this syndrome.

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CRediT authorship contribution statement

Dixit: Conceptualization, Writing – Original Draft, Writing – Review and Editing. **Churchill**: Conceptualization, Writing – Original Draft, Writing – Review and Editing. **Nsair**: Writing – Review and Editing. **Hsu**: Conceptualization, Supervision, Writing – Review and Editing.

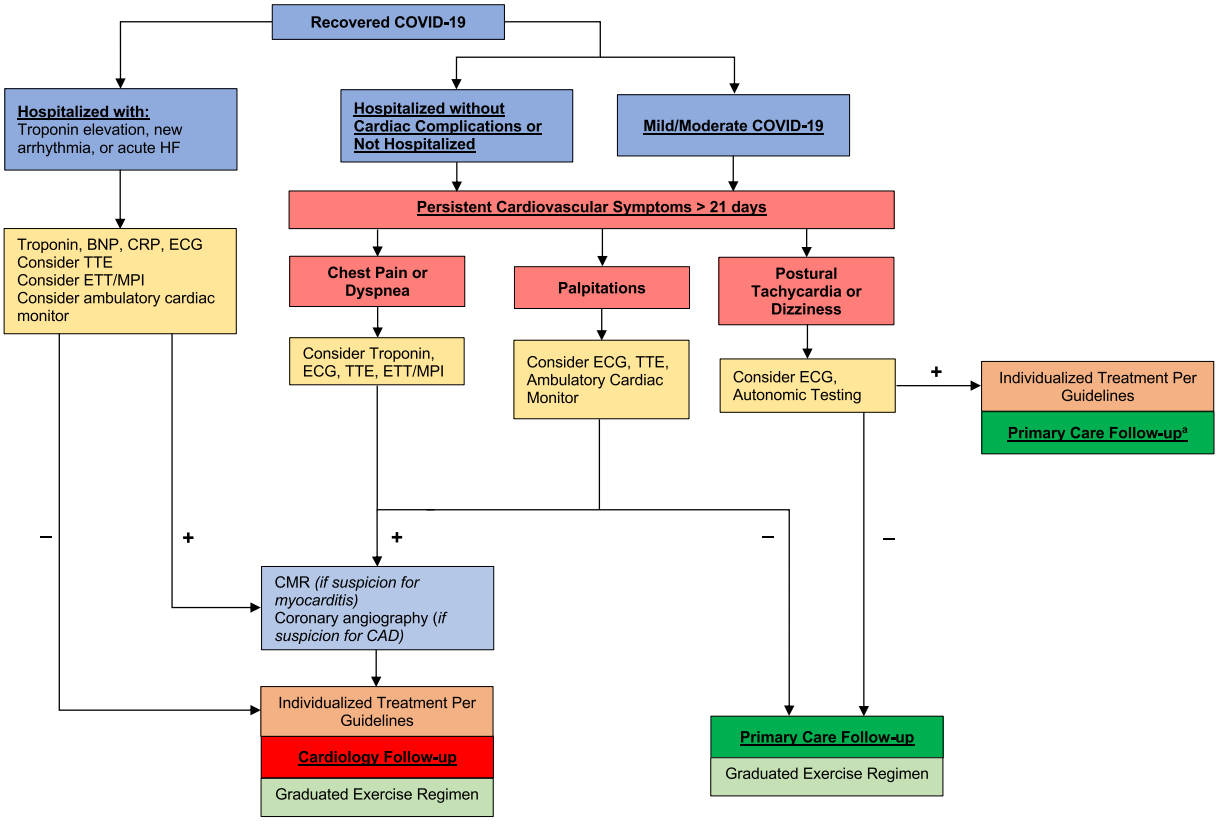

Fig. 1. Proposed algorithm for management of COVID-19 recovered patients with persistent cardiovascular symptoms or a previous COVID-19 hospitalization with cardiac complications.

[a]POTS can generally be managed by primary care physicians, but in atypical or refractory cases, referral to a cardiologist or neurologist is advised.

Abbreviations: BNP, brain natriuretic-peptide; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CRP, C-reactive protein; ECG, electrocardiogram; ETT, exercise treadmill test; HF, heart failure; MPI, myocardial perfusion imaging; POTS, Postural Orthostatic Tachycardia Syndrome; TTE, transthoracic echocardiogram.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2021.100025.

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