Chapter

Cardiovascular Post-Acute COVID-19 Syndrome: Definition, Clinical Scenarios, Diagnosis, and Management

Claudio Stefano Centorbi, Enrica Garau, Leonardo Borsi, Valerio Brambilla, Lorenzo Brambilla and Davide Lazzeroni

Abstract

Post-acute COVID-19 syndrome (PACS) describes the clinical condition of some SARS-CoV-2-infected patients in which a wide range of signs and symptoms that persist for several months after the acute phase of the disease. Cardiovascular symptoms including chest pain, dyspnea, elevated blood pressure, palpitations, inappropriate tachycardia, fatigue, and exercise intolerance are common in this condition. Some infected patients develop cardiovascular diseases such as myocarditis, pericarditis, new or worsening myocardial ischemia due to obstructive coronary artery disease, microvascular dysfunction, stress cardiomyopathy, thromboembolism, cardiovascular sequelae of pulmonary disease, arrhythmias, while others have cardiovascular symptoms without objective evidence of cardiovascular abnormalities. In the present chapter, definition, spectrum of manifestations, clinical scenarios, diagnosis, management, and therapy of cardiovascular PACS will be discussed.

Keywords: SARS-CoV2, COVID-19, post-acute COVID-19 syndrome, long-COVID-19, cardiovascular disease, myocardial injury, cardiopulmonary exercise testing, postural orthostatic tachycardia syndrome, post-COVID-19 rehabilitation

1. Introduction

1.1 Post-acute COVID-19 syndrome introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for coronavirus disease 2019 (COVID-19), has caused morbidity and mortality at an unprecedented level worldwide [1]. Scientific interest is progressively shifting from the acute phase toward the subacute and long-term consequences of COVID-19, which can affect many organ systems [2]. As replication-competent SARS-CoV-2 has not been isolated after 3 weeks, literature defined post-acute COVID-19 syndrome (PACS) as "persistent symptoms and/or delayed or long-term

complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms" [3], which can be further divided into two categories:

- Subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4 to 12 weeks beyond acute COVID-19;

- Chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses [4–6].

A large constellation of symptoms has been associated with PACS, of which the most common include fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%) [3]. Moreover, more than half of patients experiencing three or more symptoms [7]. Long COVID was the first term used to describe the range of signs and symptoms that can appear suddenly and last for months to years after SARS-CoV-2 infection [8]. The patient community as a whole coined this phrase in the spring of 2020 [9], and others such as post-COVID-19 condition, post-acute sequelae of SARS-CoV-2 infection, and post-COVID syndrome soon followed. Patients-researchers with long COVID, later known as the Patient-Led Research Collaborative, wrote the first article on prolonged symptoms of COVID-19, and long COVID continues to be the term of choice for patients [10]. As a result, the diagnostic criteria and outcomes employed vary greatly. The WHO, the UK National Institute for Health and Care Excellence, and the US Centres for Disease Control and Prevention are just a few organizations that have developed their own terminologies and definitions [11, 12]. It is noteworthy that long COVID is still frequently used by researchers as a fairly general word covering persistent signs and symptoms that remain or emerge after acute SARS-CoV-2 infection for any amount of time, while other names have much more specific definitions [13]. This highlights how, although long COVID is not always caused by viral persistence, it is difficult to determine with precision when acute COVID-19 ends [13]. Moreover, data about the length of long-term viral persistence are limited, a further item leading to lack of concordance between researchers. **Table 1** summarized different terms used to describe post-COVID-19 sequelae (**Table 1**).

Since there is a lack of universally accepted diagnostic criteria, the exact epidemiology of PACS is still not known, and the prevalence rates are extremely different between COVID-19 severity, different world area, different pandemic waves or viral variants as well as between different samples. For these reasons, differences in prevalence data of PACS may range from 30 to 90% of patients [3]. **Figure 1** shows different post-COVID-19 nomenclatures and typical post-acute COVID-19 symptoms arranged within the shape of SARS-CoV2.

1.2 Post-acute COVID-19 syndrome and cardiovascular disease introduction

The first case of SARS-CoV-2 was discovered on December 31, 2019, in Wuhan, China. In March 2020, the COVID-19 pandemic's epicenter began to shift to Latin America, Europe, and the United States. Cardiac symptoms, such as chest pain, fatigue, shortness of breath, and palpitations, might last for months in some SARS-CoV-2 patients [14]. Myocardial injury and involvement have been seen in both symptomatic and asymptomatic individuals [14]. This evidence has been seen in both

Nomenclature	Definition
Long COVID	Can be broadly defined as «signs, symptoms, and sequelae that continue or develop after acute COVID-19 or SARS-CoV-2 infection for any period of time»
Post-acute-COVID-19 syndrome	Persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms.
	The term is further divided into two categories: 1. subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities present from 4–12 weeks beyond acute COVID-19: 2. chronic or post-COVID-19 syndrome, which includes symptoms and abnormalities persisting or present beyond 12 weeks of the onset of acute COVID-19 and not attributable to alternative diagnoses.
Post-COVID-19 condition	Post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis; symptoms might be new onset after initial recovery from an acute COVID-19 episode or persist from the initial illness; symptoms might also fluctuate or relapse over time; a separate definition might be applicable for children
Persistent symptoms or COVID-19 consequences	Persistent signs and symptoms that continue or develop after acute COVID-19 for any period of time
C0VlD-19 long haulers	Common term used to refer to subjects with post-COVID-19 conditions or long COVID-19.
Ongoing symptomatic C0V1D-19	Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks
Post-acute sequelae of SARS CoV-2 infection	Persistent or new symptoms after COVID-19 infection; the definition will be revised in an iterative manner based on existing data, medical literature, and feedback from patient representatives, patients, and the scientific community; updated definitions might be used to implement a strategy to modify deeper phenotyping
Post-COVID conditions	An umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection.

Table 1.
Post-COVID-19 nomenclature.

laboratory and imaging studies, and patients hospitalized for COVID-19 have been shown to have a variety of cardiac testing abnormalities (such as electrocardiographic abnormalities and elevated cardiac biomarkers), as well as a variety of cardiovascular complications (such as myocardial damage, thrombosis, and arrhythmia) [15–18]. The literature is starting to define the specific types of Cardiovascular disease (CVD), such as myocardial injury, arrhythmias, heart failure (HF), vascular dysfunction, and thromboembolic disease, that appear to be a consequence of severe infection. Comorbid CVD has been linked to a more severe course and increased mortality of COVID-19, according to numerous studies [19–22]. A meta-analysis by Figliozzi et al. revealed that having a history of CVD tripled the odds of developing a severe course of COVID-19, which was defined as death, severe COVID-19 infection, hospitalization in an intensive care unit (ICU), use of mechanical ventilation, or disease progression [23]. Congestive HF was discovered as a potential outcome of a COVID-19 as well as a risk factor for a more severe course and greater mortality [24]. Moreover, in

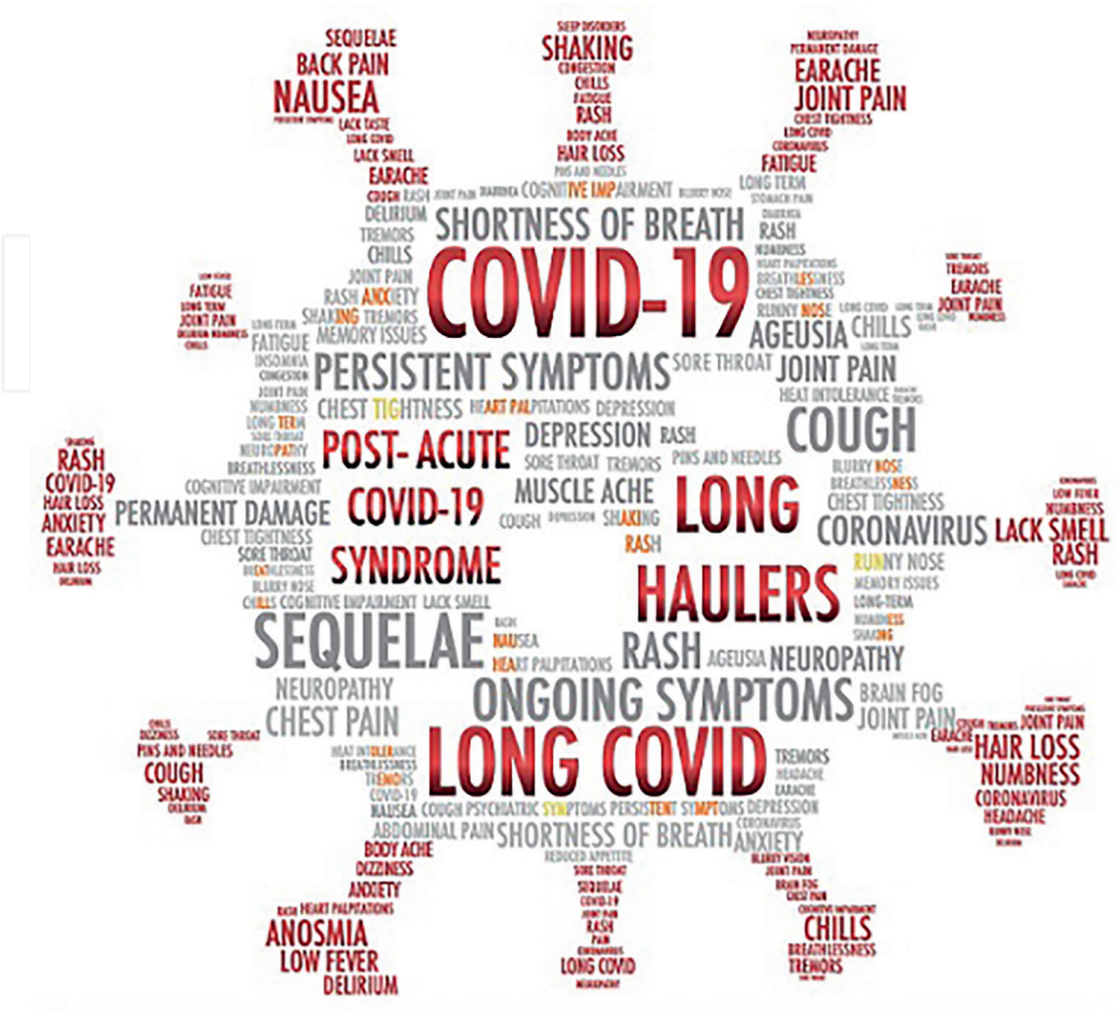

Figure 1.
Different post-COVID-19 nomenclatures and typical post-acute COVID-19 symptoms arranged within the shape of SARS.

comparison with CVD, CV risk factors are linked to a higher probability of a more severe course and a higher mortality. Different studies reported how diabetes mellitus, chronic kidney disease, and hypertension are linked to COVID-19 and PACS [25–28]. However, prognostic factors of COVID-19 severity still represent a scientific challenge, since even subjects with the same genotype and infected by the same virus may show marked difference in disease severity [29].

2. Cardiovascular PACS: pathophysiology and spectrum of diseases

PACS describe constellation of new, returning, or persistent symptoms experienced by patients 4 or more weeks after SARS-CoV-2 infection [30]. Patients with this condition can experience potentially wide-ranging symptoms of every organ system with varying impacts on quality of life. COVID-19 caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but, in addition to systemic and respiratory complications, may manifest acute cardiovascular syndrome and myocardial involvement (**Figure 2**).

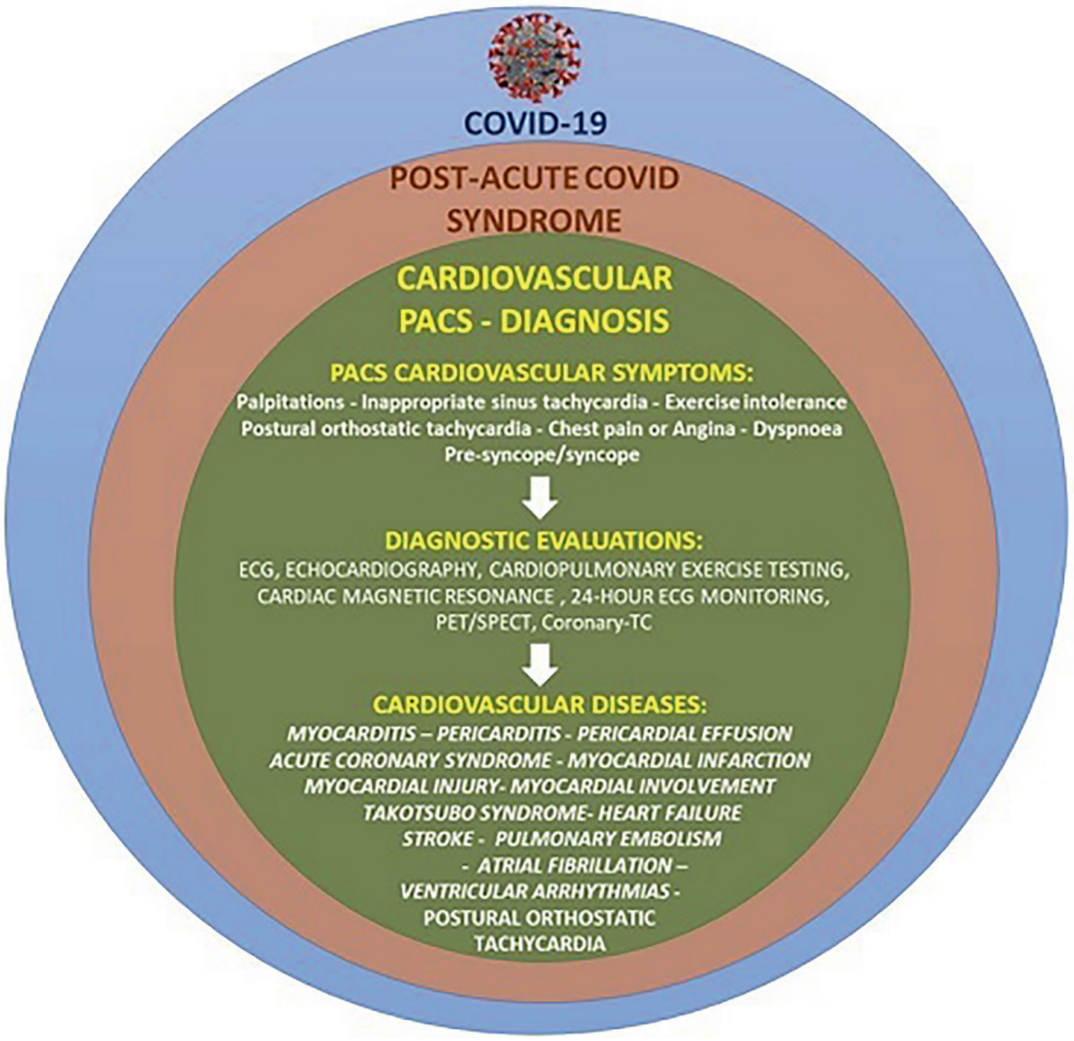

Figure 2.
From COVID-19 to PACS cardiovascular symptoms and cardiovascular disease.

During the acute phase, several mechanisms have been proposed to directly or indirectly justify myocardial injury:

- direct cytotoxic injury [31]
- dysregulation of renin–angiotensin–aldosterone system or autonomic function [32]
- endothelitis and thrombo-inflammation [33]
- dysregulated immune response with cytokine release [34]

SARS-CoV-2 binds on transmembrane angiotensin-converting enzyme 2 (ACE2) to enter in the host cells including type 2 pneumocytes, macrophages, endothelial cells, pericytes, and cardiac myocytes, leading to inflammation and multiorgan failure. The infection of endothelial cells or pericytes could lead to microvascular and macrovascular dysfunction with intravascular thrombosis. The immune

over-reactivity contributes to potentially destabilize atherosclerotic plaques and explain the possible development of the acute coronary syndrome. The progression of systemic inflammation and immune cell overactivation, leading to a "cytokine storm" (abnormal elevated level of cytokines) in infection of the respiratory tract and particularly of type 2 pneumocytes, leads to severe acute respiratory syndrome. It has been demonstrated that activated T cells and macrophages may infiltrate infected myocardium, thereby resulting in the development of myocarditis. Similarly, the viral invasion could cause directly myocyte damage and contribute to the development of arrhythmias and left ventricular dysfunction [14]. The pattern of myocardial injury following SARS-CoV-2 infection was initially derived from autopsy. In early autopsy series of 80 consecutive SARS-CoV-2 PCR-positive cases, only four patients (5%) had definition of cardiac injury [35]. In a subsequent autopsy study, a definite diagnosis of myocarditis was demonstrated in 7, 2, to 14% of cases, while interstitial macrophage infiltration was found in 86% of patients, pericarditis and right ventricular injury in 19%, respectively [36, 37]. However, subsequent studies demonstrated that only 1.4% met the well-established histological criteria [38] for myocarditis, suggesting that true myocarditis was relatively rare [39–41]. Lindner et al. [42] demonstrated the presence of SARS-CoV-2 viral particles in the hearts and in particular in interstitial cells including pericytes and macrophages and not within cardiomyocytes.

Cardiac troponin is frequently elevated in COVID-19 patients [43] and indicates myocardial injury. As a consequence of the above-mentioned mechanisms, myocardial injury during COVID-19 includes myocarditis and pericarditis [44], acute coronary syndrome secondary to obstructive coronary artery disease (myocardial infarction type 1) [45] or to oxygen augmented demand (myocardial infarction type 2) [45–49], multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A) [50–52], takotsubo/stress cardiomyopathy [53, 54], acute or pulmonale resulting from macro-pulmonary or micro-pulmonary emboli [45, 55], exacerbation of chronic conditions like preexisting heart failure or acute viral infection unmasking subclinical heart disease [56–60]. Since more of these etiologies may coexist, identifying a specific underlying cause during acute phase sometimes may be really challenging.

After the acute phase, PACS may occur in patients who have experienced varying degrees of COVID-19-related disease, from asymptomatic infection to critical illness. Chest pain, dyspnea, and palpitations are some of the key symptoms that draw attention to the cardiovascular system. These symptoms may underlie a COVID-19-related cardiovascular disease that developed or exacerbated during or after infection. For this reason, it is therefore necessary to distinguish cardiovascular complications that can occur during the early post-acute or in chronic phase of COVID-19 (post-acute COVID-19 syndrome with cardiovascular disease, PACS-CVD) from cardiovascular symptoms that extend beyond acute infection, but which are not correlated with a cardiovascular disease (post-acute COVID-19 syndrome with cardiovascular symptoms, PACS-CVS) [61].

Mechanisms for the development of cardiovascular disease after COVID-19 infection are still poorly understood, and several hypotheses have been suggested:

- chronic inflammatory response evoked by persistent viral reservoirs in the heart following the acute infection with consequent tissue damage and chronic myocardial fibrosis that leads to impaired ventricular compliance, perfusion, stiffness, contractility and potential arrhythmias [62].

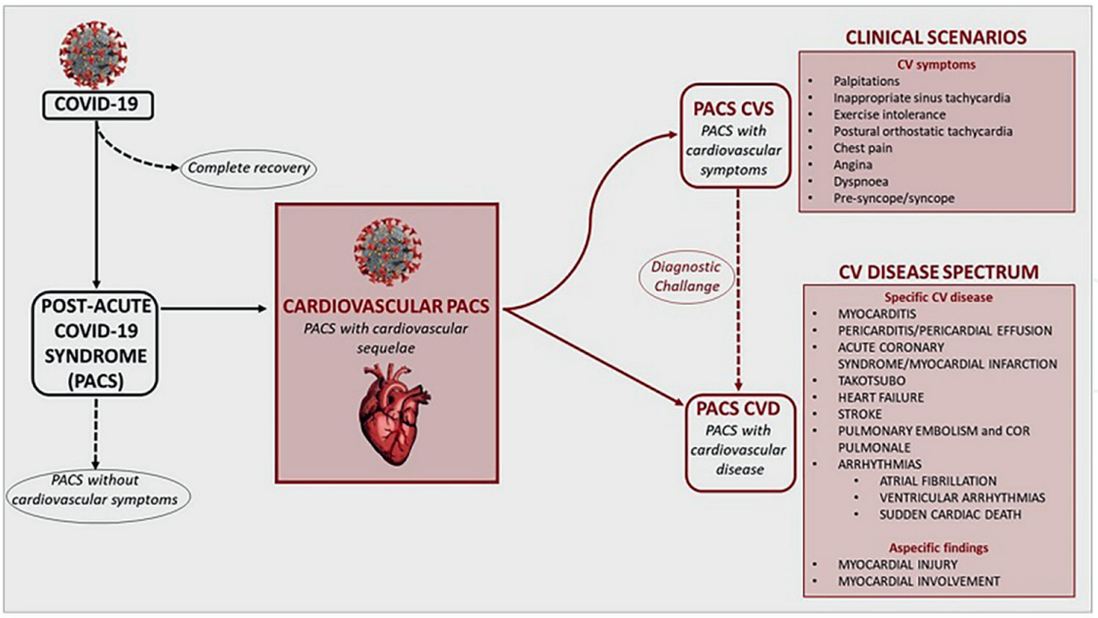

Figure 3.
PACS cardiovascular symptoms and PACS cardiovascular disease.

- autoimmune response to cardiac antigens through molecular mimicry [63]. In fact, Wang et al. identify a wide range of autoantibodies against humoral and tissue antigens in patients with severe COVID-19 [64–66]; in other studies, autoantibodies against cholinergic and adrenergic receptors were found [67, 68]. Moreover, cytokine profile analysis and proteomic studies revealed increased expression of prothrombotic factors beyond acute infection [69, 70], thereby justifying increased rate of thrombo-embolic events and/or pulmonary hypertension.

Figure 3 shows differences between PACS with cardiovascular symptoms and cardiovascular disease as well as different clinical scenarios and disease spectrum of cardiovascular PACS.

2.1 PACS-cardiovascular disease

CVD refers cardiovascular conditions that manifest 4 weeks after SARS-CoV-2 infection and includes all forms of myocardial involvement that can be development during acute phase of infection:

- Myocarditis
- Pericarditis
- New or worsening myocardial ischemia due to obstructive coronary artery disease, augmented demand, or microvascular dysfunction (acute coronary syndrome and myocardial infarction)
- Stress cardiomyopathy (Takotsubo syndrome)
- Thromboembolism and cardiovascular involvement of pulmonary disease (e.g. pulmonary hypertension with right ventricular failure)

- Multisystem inflammatory syndrome in adults (MIS-A) and children (MIS-C).
- Arrhythmias (e.g. atrial fibrillation (AF), premature ventricular beats, and ventricular tachycardias).

Discerning whether PACS-CVD began in acute infection, during illness resolution, or as a new condition post-recovery may be challenging.

- **Myocarditis:** it is defined by the presence of cardiac symptoms such as chest pain, dyspnea, palpitations, and syncope associated with:
  - Laboratory: elevated cardiac troponin;
  - Electrocardiogram (ECG): abnormal electrocardiographic findings (diffuse T-wave inversion and ST segment elevation);
  - Echocardiography: left ventricular wall motion abnormalities in noncoronary distribution;
  - cardiac magnetic resonance (CMR) patterns: non-ischemic late gadolinium enhancement pattern (usually sub-epicardial) with prolonged native T1 and T2 relaxation times;
  - Histopathologic findings on biopsy or postmortem evaluation: inflammatory myocardial infiltrates associated with myocyte degeneration and necrosis;
  - Absence of critical epicardial coronary artery disease (defined using noninvasive coronary imaging and or coronary angiography).

Prevalence and incidence of myocarditis in COVID-19 infection are highly variable [71]. Autopsy results among COVID-19 patients showed mixed data. In a study by Halushka et al, classic myocarditis was identified in 7.2%, non-myocarditis inflammatory infiltrate in 12.6%, single-cell ischemia in 13.7%, and acute myocardial infarction in 4.7% [72]. Regarding echocardiographic data in patients hospitalized for COVID-19 suggest that myocardial dysfunction may be present in up to 40% [73, 74]. On the other hand, cardiac magnetic resonance (CMR), the most sensitive imaging modality for identifying myocardial (and pericardial) involvement, has been used in several studies to evaluate symptomatic and asymptomatic individuals with COVID-19, in both hospital and ambulatory settings. In a study of 100 patients (33% hospitalized), non-ischemic LGE was found in 20% and prolonged native T1 and T2 relaxation times in 73% and 60%, respectively [75]. Similar findings have been observed in other CMR studies, with variable degrees of LGE and mapping abnormalities [76–81]. When performed in athletes as screening protocol, various abnormalities have been noted with 0.6–3% of subjects meeting modified Lake Louise criteria for clinical myocarditis [82–84]. Variability in observed findings with CMR likely reflects differences in the populations studied, in timing of CMR relative to infection onset as well as in the specific imaging protocols that could affect interpretations of imaging data. Several mechanisms have been proposed

by which SARS-CoV-2 may contribute to myocarditis such as direct virus invasion, host inflammatory or immune responses, and microvascular angiopathy. Moreover, emerging data seem to indicate other mechanisms such as a maladaptive host immune response with excessive activation of innate immune pathways, a surge of pro-inflammatory cytokines, a deregulated thrombo-inflammation, a thrombotic microangiopathy, an endothelial dysfunction, and a mechanism of molecular mimicry [85–88]. Other hypotheses may include augmented demand ischemia, stress cardiomyopathy, and hypoxia-induced myocardial injury [89]. While the acute inflammation and myocardial injury have been well attended, the long-term effects of myocarditis are completely unknown. Most infected patients experience mild form of myocarditis with self-limiting symptoms and without persistence of LGE; other patients, in the chronic phase, experience various degrees of systolic dysfunction (with symptoms related to heart failure) and/or cardiac arrhythmias (e.g. atrial fibrillation, supraventricular, and/or ventricular tachyarrhythmias) because of extensive myocardial fibrosis [90, 91].

- **Pericarditis:** it represents another cardiac manifestation of COVID-19 and is defined by the presence of two or more of the following features [92]:

  - pericardial chest pain;

  - pericardial friction rub;

  - PR depression and or diffuse concave upward ST elevation on ECG;

  - new or worsening pericardial effusion during infection.

  In some cases, it may be associated with myocardial involvement (myo-pericarditis). The pathogenesis of acute and chronic pericarditis and myo-pericarditis in COVID-19 patients is not still understood. Direct virus-mediated cytotoxicity and dysregulation of the immune system are the key in the pathogenesis of SARS-CoV-2 infection leading to an overproduction of pro-inflammatory cytokines resulting a cytokine storm, an immune-mediated inflammation that affects myocardium and pericardium and an ACE 2 receptor downregulation in acute and long COVID-19 play a fundamental role in pericardial involvement [93, 94]. Data on pericardial disease are relatively scarce. A systematic review including studies on adult patients undergoing any type of cardiac assessment after COVID-19 recovery reported a prevalence of pericardial enhancement in 63/758 patients (8%) and of pericardial effusion in 99/758 patients (13%) [95]. Only few studies reported a formal clinical diagnosis of myo-pericarditis (2%) and pericarditis (0.5%) [96]. Based on studies, pericarditis appears to be common in the acute infection but rare in the post-acute period of COVID-19, while small pericardial effusions may be relatively common in the post-acute phase of COVID-19 [97]. In hospitalized patients with COVID-19, diffuse acute ST changes consistent with pericarditis were present in 12% of subjects [98]. In competitive athletes screened after COVID-19, pericarditis was present in 0.3% of cases [99]. In the post-acute period of COVID-19, a pericardial effusion was identified in a proportion of patients ranging from 5 to 20% [100, 101].

- **Myocardial ischemia:** Virus damage of endothelial cells or pericytes leads to microvascular and macrovascular dysfunction [102], thereby potentially destabilizes atherosclerotic plaques. Moreover, hypercoagulability state linked to inflammation also predisposes to intravascular thrombosis. All these mechanisms may explain acute coronary events that occur during the acute phase of infection such as acute coronary syndrome with myocardial infarction type 1 secondary to atherosclerotic plaque instability or intravascular thrombosis. Arrhythmias or systemic hypoxia also contribute to augmented oxygen demand and may cause myocardial injury with myocardial infarction type 2 (without obstructive coronary disease). During acute phase, myocardial injury, assessed by troponin elevation, complicate a share of hospitalized patients with COVID-19, particularly patients who require intensive care. In post-infection phase, patients could experience signs and symptoms of inducible ischemia due to the instability of an unknown or known critical epicardial coronary artery disease, or due to the presence of coronary microvascular dysfunction in the absence of obstructive coronary artery disease [61]. About 20–30% of patients hospitalized with COVID-19 show elevations in troponin levels, often because of myocardial infarction type 2 that is the most common manifestation of myocardial injury during infection [103, 104]. The real risk of ACS and of myocardial injury in the setting of post-COVID-19 infection is unknown.

- **Stress-induced cardiomyopathy (Takotsubo syndrome):** it represents a clinical syndrome characterized by a transient reversible wall motion abnormality of the left ventricle in the absence of significant obstructive coronary artery disease [105]. Takotsubo syndrome is typically associated with intense emotional or physical stress and is most commonly in women (>90%). The pathophysiology of Takotsubo syndrome is not well understood. It seems that intense sympathetic overstimulation by catecholamines (catecholamine-mediated myocardial stunning) results in myocardial stunning as a direct effect of catecholamines on cardiomyocytes, hyperdynamic contractility, epicardial spasm, and microvascular dysfunction [106]; moreover, autonomic dysfunction may persist long after the acute phase of Takotsubo [107]. Some reports have demonstrated that Takotsubo cardiomyopathy represents a complication of COVID-19 [108, 109]. It is noteworthy that all patients with COVID-19, in addition to typical predisposing/triggering factors for Takotsubo syndrome (e.g. hyperadrenergic tone or microvascular/endothelial dysfunction), experience a strong emotional stress linked to the fear of the potentially lethal consequences of the infection (emotional stress) [110, 111]. Emblematic and curious is the case of a patient with a previous history of anxiety, who, during a hospitalization for COVID-19, develops a Takotsubo syndrome immediately after the communication of the death of her husband, also hospitalized for COVID-19 [112]. Interesting studies have showed that patients with COVID-19 can have high level of cortisol, higher than patients undergoing major surgery [113]. The high levels of cortisol and catecholamines can have a "toxic" effect on cardiomyocytes in COVID-19 patients and could play a role in the development of Takotsubo syndrome [114]. Although tending to have a benign prognosis, during the acute phase Takotsubo syndrome may be complicated with severe ventricular systolic dysfunction, severe mitral insufficiency resulting in signs and symptoms of heart failure/cardiogenic shock, obstruction of the outflow tract of the left ventricle, intracavitary thrombosis,

and atrial and ventricular arrhythmias. It is also known that recovery of ventricular function can be variable over time and that, in the long-term, myocardial fibrosis can be observed despite complete recovery of the systolic function of the left ventricle [115]. In post-COVID-19 phase, patients may experience persistence of signs and symptoms of heart failure with or without complete recovery of systolic function and the onset or persistence of arrhythmias often linked to the presence of myocardial fibrosis.

- **Thromboembolism and cardiovascular sequelae of pulmonary disease:** The most severe form of COVID-19-associated with interstitial pneumonia is the acute respiratory distress syndrome (ARDS) [116]. Precapillary pulmonary hypertension is a frequent finding attributed to hypoxic pulmonary vasoconstriction, microvascular thrombosis, and sometimes pulmonary vascular remodeling [117]. The reflex vascular regulation of the pulmonary circulation in the presence of poorly oxygenated areas can significantly reduce the blood flow directed to atelectatic areas to improve the ventilation/perfusion ratio increasing right ventricular afterload [118]. On the other hand, COVID-19 infection exposes to a greater risk of venous thromboembolisms. About 20% of patients with COVID-19 shows coagulation abnormalities, which might cause venous and pulmonary thromboembolism [119], from segmental and subsegmental pulmonary embolisms (often pauci-symptomatic) to bilateral pulmonary embolisms with further deterioration of gas exchanges [120–122], thereby leading to acute right heart failure [123]. Cardiac involvement may involve varying degrees of right ventricular systolic dysfunction up to cardiogenic shock with hemodynamic instability. The real impact of pulmonary embolism during severe manifestations from COVID-19 is likely to be underestimated, since generally only patients in whom there is a clinical suspicion undergoes pulmonary CT angiography. However, a study revealed that 40% of COVID-19 patients with elevated D-dimer and who underwent a thoracic CT angiography had pulmonary embolism, often segmental [124]. A recent metanalysis showed that 20% of patients hospitalized for COVID-19 infection develop pulmonary embolism as a complication during hospitalization. However, it clearly emerged that only a minimal part of the patients had undergone pulmonary CT angiography indicating that the result is probably underestimated [125]. In chronic stages of infection, patients could complain of dyspnea and signs and symptoms of heart failure secondary to chronic pulmonary hypertension with right ventricular dysfunction.

- **MIS-A and MIS-C:** Systemic inflammation is one of the pathophysiological keys of COVID-19 infection. This inflammatory state often persists during the convalescent phase. This post-infection hyperinflammatory phase can lead a multisystem inflammatory syndrome that was seen for the first time in April 2020 [126–128] in pediatric population and was called multisystem inflammatory syndrome (MIS-C). Successively, a similar multisystem hyperinflammatory state was observed in adults and was called multisystem inflammatory syndrome in adults (MIS-A) [129]. The exact pathophysiology of MIS-A and MIS-C remains unclear. Possible pathophysiological the mechanisms for both syndromes include the formation of autoantibodies, antibody recognition of persistent viral antigens on infected cells and, particularly for MIS-C, hyperinflammatory response due to viral super antigens, abnormal immune response to the SARS-COV 2 virus

with some similarities to Kawasaki disease, macrophage activation syndrome, or cytokine storm. The diagnostic criteria of both syndromes are similar: a previous SARS COV2 infection and hyperinflammatory state associated with dysfunction of at least two between cardiovascular, pulmonary, gastrointestinal, cutaneous, nervous, hematological, and renal systems [130, 131]. The exact incidence of MIS-A and MIS-C is largely unknown.

- **Arrhythmias:** Arrhythmias are frequently reported in COVID-19 patients. Atrial fibrillation (AF) being the most common form. The pathophysiology of COVID-19-related AF is not well understood. Proposed mechanisms include reduction in angiotensin-converting enzyme 2 (ACE2) receptor availability, cytokine storm, direct viral endothelial damage, electrolytes, and acid base abnormalities in the acute phase of severe illness and increased adrenergic drive [132]. Based on literature data, among COVID-19 patients, AF was detected in 19–21% of all cases [133–135] and in patients with severe pneumonia, ARDS) and sepsis, the incidence of during hospitalization is usually higher [136, 137]. The real incidence of atrial fibrillation in post-COVID-19 period is unknown. Increased post-infectious adrenergic tone, any persistent cardiac involvement during infection (e.g. myocarditis and chronic pulmonary heart) or the presence of predisposing illness (e.g. arterial hypertension, ischemic heart disease, mitral regurgitation, and hypertensive heart) represent the most important predisposing factors. Management of AF should be set up according to current guidelines [138, 139]. Ventricular arrhythmias are less frequent during infection and may be caused by myocardial injury secondary to myocarditis or ischemic myocardial damage, by the presence of electrolyte or acid base imbalances or by the concomitant use of QTc-interfering drugs, especially in intensive care. In post-COVID-19 period, ventricular arrhythmias, at rest or during exercise, should represent "red flags" of cardiac involvement, even in asymptomatic patients.

2.2 PACS cardiovascular symptoms

CVS include a series of heterogeneous cardiovascular symptoms without objective evidence of cardiovascular disease using standard diagnostic tests. Exercise intolerance and tachycardia are the most common reported symptoms together to postural orthostatic tachycardia syndrome (POTS) post-exertional malaise and chronic fatigue syndrome. Chest pain and dyspnea with or without exercise intolerance including memory impairment and attention deficit with poor executive function (frequently described as brain fog) and sleep disturbance are other symptoms reported. There are not established timeline for diagnosing PACS-CVS but it should be considered when cardiovascular symptoms persist beyond a time frame typical for acute infection severity and expected recovery based on age and status of underlying health and without the evidence of cardiovascular impairment because of COVID-19 infection. Ten to 30% of patients seem to experience prolonged symptoms following SARS-CoV-2 infection related to cardiovascular system [140]. In a study one-third of patients with COVID-19 noted at least one symptom and nearly 15% experienced 3 or more symptoms lasting 12 weeks or longer [141]. Different mechanisms have been proposed for PACS-CVS: inflammation [142] immune activation [142, 143] viral persistence [144] triggering of latent viruses [145] endothelial dysfunction [146, 147] impaired exercise metabolism [148] and cardiac deconditioning following viral infection [149, 150].

2.3 Post-COVID-19 Tachycardia, exercise intolerance with post-exertional malaise and chronic fatigue syndrome

Inappropriate sinus tachycardia and exercise intolerance are often associated after COVID-19 infection. It is usually an inappropriate compensatory response that reflects dysautonomia, hyperadrenergic, and inflammatory post-infection state and the presence of metabolism alterations and immune dysfunction [151–153]. Deconditioning represents a final common pathway starting from these two conditions. There are reduced circulating volume and cardiac atrophy with a shift in the LV pressure-volume curve because of hypovolemia and reduced stroke volume with compensatory tachycardia [149–151]. Once symptoms develop, a downward spiral characterized by short periods of bedrest that produce exercise intolerance, post-exertional malaise, and tachycardia leads to further inactivity and worsening of cardiovascular deconditioning with even more debilitating symptoms and chronic fatigue [35]. Patients with COVID-19 reported at home chronic fatigue and dyspnea by 30% and 15%, respectively, at 6 months [152].

Post-COVID-19 Postural Orthostatic Tachycardia Syndrome: Inappropriate tachycardia represents one of the most common cardiovascular sequelae of PACS as well as the most common cause of exercise intolerance in individuals without exertional desaturation. Symptoms often include both cardiac symptoms (palpitations, light-headedness, chest discomfort, dyspnea, or pre-syncope) and non-cardiac symptoms (brain fog, headache, nausea, tremulousness, blurred vision, and exercise intolerance or fatigue) [153]. The presence of inappropriate tachycardia may result in significant limitations on functional capacity as well as in daily living activities such as doing housework or bathing [154]. In the absence of orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS) is defined by an increase in heart rate of >30 beats per minute in those aged >19 years or >40 beats per minute in those aged 120 beats per minute during the 10-minute active stand test. Orthostatic hypotension is defined by a drop in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 min of standing [154]. Figure shows symptoms, diagnostic criteria, mechanisms, and therapy of post-COVID-19 POTS as well as a tachogram and autonomic function data of a case of post-COVID-19 male with symptomatic POTS due to hyper-adrenergic response to orthostatic position (**Figure 4**).

Under normal conditions, the assumption of upright posture affects an instantaneous shift of ≈500 mL of blood from the thorax to the lower abdomen and legs, a secondary shift of plasma volume (10–25%) out of the vasculature and into the interstitial tissue, which decreases venous return to the heart (preload), and further affects a decline in cardiac filling and BP [154]. In response of preload reduction, in order to maintain blood pressure homeostasis, the baroreceptors trigger a compensatory decrease in parasympathetic tone as well as an increase in sympathetic activation, that result in an increase in HR and systemic vasoconstriction [154]. The net hemodynamic effect of transition to upright posture is a 10- to 20-bpm increase in HR, a negligible change in systolic BP, and a ≈5-mmHg increase in diastolic BP [149]. Orthostatic dysregulation occurs when this gravitational regulatory mechanism does not respond properly. Patients can present with orthostatic hypotension (seen in autonomic nervous system failure) or with orthostatic tachycardia [154]. Patients with POTS typically maintain (or even increase) their BP on standing. The cardinal hemodynamic feature in POTS is that HR increases excessively and is associated with multiple symptoms on standing that improve with recumbence [154]. Of note,

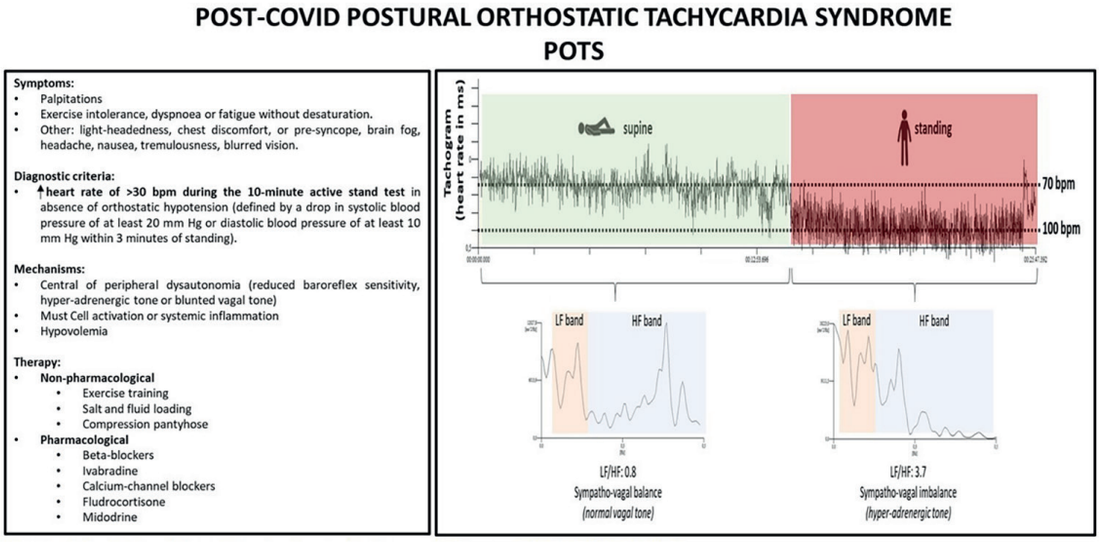

Figure 4.
Evaluation, diagnostic criteria, mechanisms, and therapy of post-COVID POTS.

tachycardia should last for more than 30 to induce symptoms. It is also important that the patient stands quietly for the full 10 min, as an increase in heart rate may take time. Initial evaluation requires supine blood pressure, saturation, and heart rate measurements, followed by periodic re-assessment in standing position as well as during a 6-minute walking test. Exercise testing should also recommend in patients with exercise intolerance, especially in those with chest pain or discomfort; cardio-pulmonary exercise testing (CPET) could be useful in order to evaluate patients with exercise intolerance and dyspnea, since it allows to differentiate between cardiac, pulmonary, or peripheral causes. Ambulatory rhythm monitoring should also be considered to exclude arrhythmia and define the pattern of heart rate elevation [61]. Whereas the latter can likely be done with a 24- to 48-hour Holter monitor, longer-duration monitoring (e.g. extended Holter monitor and event monitor) should be considered in those with episodic palpitations, depending on their reported frequency [61]. Mobile health devices capable of heart rate and ECG monitoring can also help in evaluation and surveillance monitoring during recovery [61]. **Figure 5** shows pro-posed diagnostic workup for post-COVID-19 POTS.

The benefits of exercise training following bedrest deconditioning and that resulting from POTS [155–158] are well described. To achieve these effects, however, specific types of exercise training are recommended. For patients unable to tolerate upright exercise, recumbent or semi-recumbent exercise (e.g. rowing, swimming, or cycling) is recommended initially, with transition to upright exercise over time as orthostatic intolerance resolves [159, 160]. Exercise duration should be short initially and increased gradually as functional capacity increases, with submaximal level of intensity. In fact, since autonomic dysfunction represents the main cause of POTS, physical exercise represents the most powerful therapy able to positive modulate autonomic function, thereby improving functional capacity, even in the presence of cardiovascular disease [161]. Other non-pharmacological interventions should be also considered such as: salt and fluid loading (5–10 g or 1–2 teaspoons of table salt per day as well as 2–3 liters of water or an electrolyte-balanced fluid per day), support stock-ings, avoid factors that contribute to dehydration (alcohol and/or caffeine, excessive heat exposure [162]. Although no pharmacological therapies are currently approved

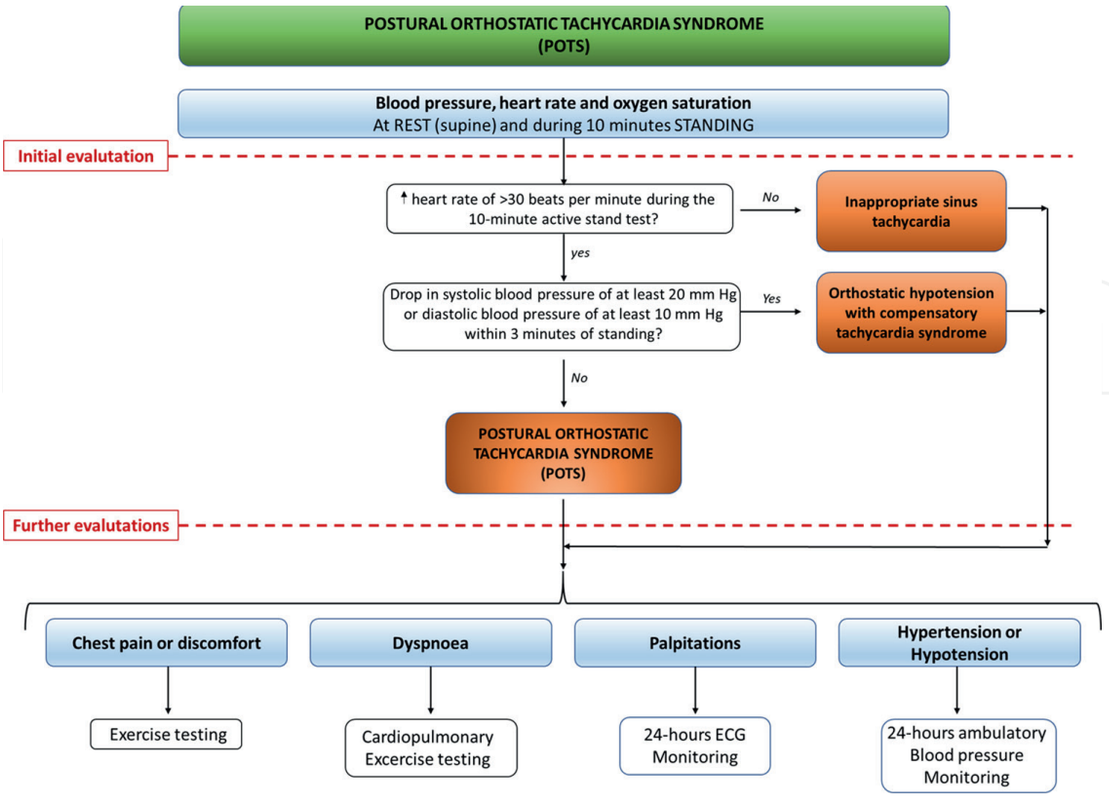

Figure 5.
Diagnostic work-up for post-COVID POTS.

for POTS treatment in PAC, low-dose beta-blocker (e.g. bisoprolol, metoprolol, nebivolol, and propranolol) or a non-dihydropyridine calcium-channel blocker (e.g. diltiazem and verapamil) may be used empirically in order to slow heart rate. On the other hand, nonselective beta-blockers (e.g. propranolol) may help to control symptoms in POTS patients [163, 164], especially in those with coexisting anxiety or migraine. Moreover, ivabradine has also been used in those with severe fatigue exacerbated by beta-blockers and calcium-channel blockers. A trial of 22 patients with POTS an improvement in heart rate and quality of life was observed following treatment with ivabradine for 1 month [165]. Fludrocortisone (up to 0.2 mg taken at night) may also be used in conjunction with salt loading to increase blood volume and help with orthostatic intolerance (AHA). Finally, midodrine (2.5–10 mg) may help with orthostatic intolerance, with the first dose taken in the morning before getting out of bed and the last dose taken no later than 4 pm [162].

2.4 Post-COVID-19 angina or chest pain

Chest pain represents one of the symptoms most frequently encountered in patients with previous Sars-Cov-2 infection. Ischemic chest pain (angina) can be related to coronary involvement by thrombotic or vasospasm mechanism or microvascular disease, instead non-ischemic chest pain can be found in the case of pericarditis or myocarditis. Sometimes, non-cardiac chest pain can be experienced by originating from the lungs or pulmonary circulation, aorta or mediastinum for lymphadenitis. A careful anamnesis on the characteristics of the symptom allows to address the diagnostic workup (see figure work-up). Troponin values together with the ECG and echocardiogram must be used to exclude the hypothesis of ischemic or

non-ischemic myocardial injury. Stress test, better if cardiopulmonary exercise testing, allows to highlight inducible ischemia as well as to differentiate between cardiac, peripheral, or ventilatory causes of chest pain. Echocardiography or myocardial scintigraphy (SPECT) with pharmacological or physical stress in association with anatomical study of coronary artery with angio-TC or invasive coronary angiography allow the diagnosis of obstructive or microcirculatory coronary disease in specific cases. Particularly if microvascular dysfunction is suspected, Positron Emission Tomography (PET) for myocardial perfusion assessment may be particularly useful [166, 167]. Finally, invasive coronary vasomotor test helps in coronary vasospasm evaluation, but it must be performed in specialized centers [166, 167]. In the case of non-cardiac chest pain, anatomical study (chest X-ray, chest CT, and possible pulmonary angio-TC) associated with a functional study (arterial O2 saturation, resting spirometry, and cardiopulmonary exercise testing) together with the determination of the D-dimer can help to identify any thrombo-embolic or pulmonary parenchymal disease resulting from COVID-19 infection. Additional targeted diagnostics examination such as chest angio-TC or PET study must be reserved for patients with specific diagnostic suspicions such as aortic or mediastinal disease.

2.5 Post-COVID-19 dyspnea

Since lung disease represents the major manifestation of SARS-COV2, a careful cardio-respiratory physical examination represents the first assessment to investigate causes of post-COVID-19 dyspnea, followed by arterial oxygen saturation (both at rest and during the 6-minute Walking Test). Subsequently, an anatomical study of the respiratory system with chest X-ray associated with a functional study with Spirometry at rest will be necessary. Chest computed tomography or computed tomography pulmonary angiogram should be reserved for patients with highly suspicious and/or suggestive findings of significant pulmonary, parenchymal, and/or vascular involvement (history of moderate or severe COVID-19-related disease, elevated D-dimer levels during the acute phase, risk factors for venous thromboembolism). When pulmonary causes were excluded, the diagnostic process must include the study of the cardiovascular system (see figure work-up). ECG allows to exclude cardiac rhythm abnormalities (e.g., tachyarrhythmias such as atrial fibrillation), new conduction abnormalities that may underlie left or right ventricular dysfunction, or to observe anomalies indicative of myocardial necrosis-ischemia. Echocardiography allows the analysis of the left ventricle and can highlight a systolic dysfunction with global or segmental kinetics anomalies suggestive for myocardial injury, giving the clinical suspicion of myocarditis or ischemic event. Right ventricular dilatation and systolic dysfunction associated with pulmonary hypertension and dilated pulmonary circulation may be suggestive of pulmonary thromboembolism and/or moderate or severe pulmonary parenchymal disease. Pericardial effusion may be a suggestive finding for a pericardial event. Laboratory tests with blood gas analysis may help and must include the determination of the hemoglobin values, of BNP (in the suspicion of heart failure), of the troponin values (to highlight any chronic myocardial damage), of D-dimer (in the suspect of a thrombo-embolic event or of the oxygen saturation and partial pressure values and of the acid-base balance). The most informative test for patients with post-COVID-19 dyspnea is still the cardiopulmonary exercise Testing (CPET) [168]. CPET allows to assess the presence of myocardial ischemia (reduced values of VO2/WR slope, reduced oxygen pulse, and ST abnormalities), of ventilatory dysfunction (high VE/VCO2 slope values,

trend anomalies, and PET-O2 and PET-CO2 values), of muscle-metabolic inefficiency (altered anaerobic threshold and reduced oxygen uptake extraction slope values) or aortic stiffness [169]. Moreover, post-COVID-19 unexplained dyspnea without cardiopulmonary abnormalities is common with PACS and may relate to deconditioning with poor cardiovascular fitness. In a study, 59% of patients with COVID-19 had persistent dyspnea at 3 months [170]. On Cardiopulmonary exercise testing (CPET), patients with post-COVID-19 dyspnea had lower peak VO2, lower VO2 at anaerobic threshold, and data suggestive of muscular inefficiency such as lower oxygen uptake extraction slope (**Figure 6**).

Finally, third-level assessments can be reserved for those patients with a picture that is not yet perfectly clear but is suspected of specific pathologies. If inducible ischemia is highlighted, pharmacological or exercise eco stress or myocardial scintigraphy, coronary computed tomographic angiography (CCTA) or invasive coronary angiography can be performed. Instead, if myocarditis is suspected, it will be necessary to perform a contrast-enhanced cardiovascular magnetic resonance imaging to

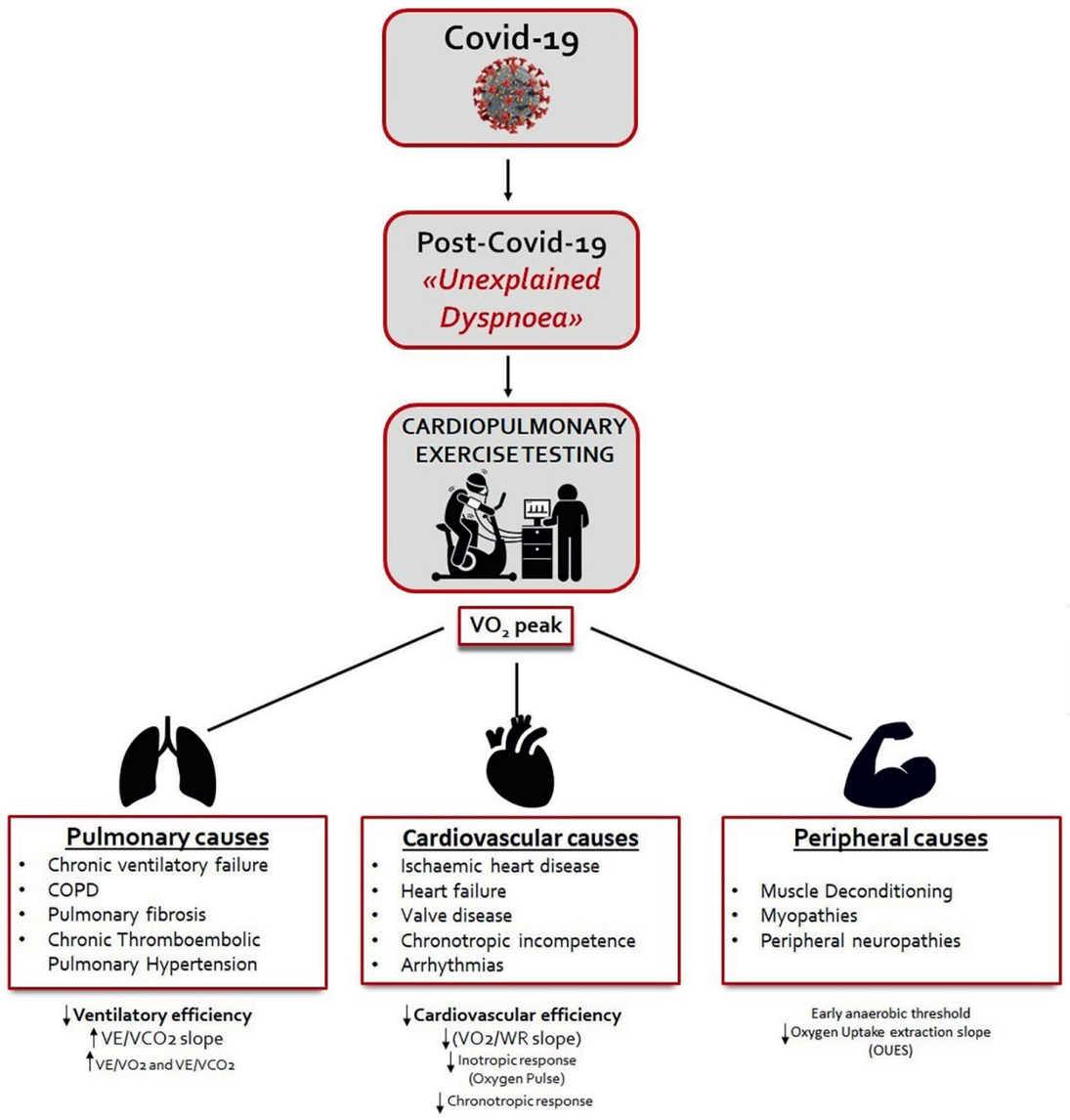

Figure 6.
Cardiopulmonary exercise testing evaluation in post-COVID patients.

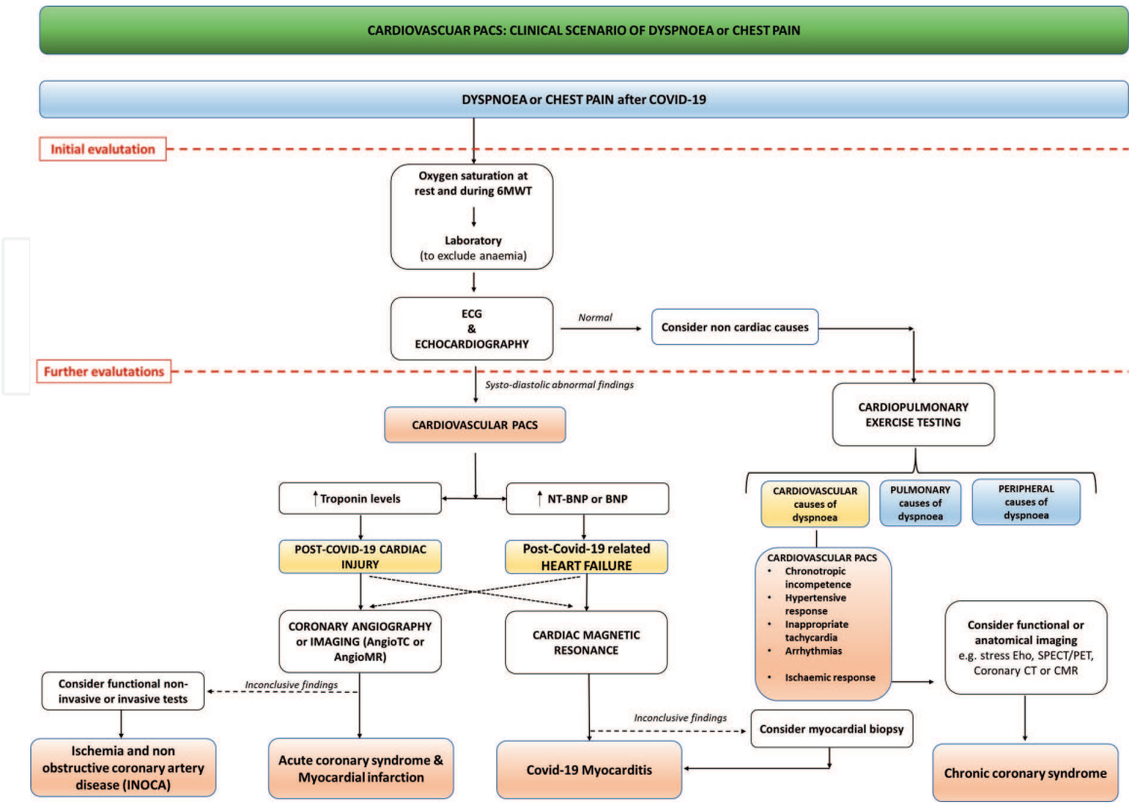

Figure 7.
Diagnostic work-up for post COVID-19 dyspnea and chest pain.

assess the possible presence of myocardial damage with myocardial fibrosis. Cardiac biopsy should be evaluated only in special cases. **Figure 7** shows proposed diagnostic workup for post-COVID-19 dyspnea and chest pain.

2.6 Post-COVID-19 fatigue

Fatigue is a typical feature of coronavirus disease 2019 (COVID-19) in both the acute and chronic phases. In a meta-analysis, the prevalence of fatigue was 23% in acute COVID-19 infection [171]. Persistence for weeks or months beyond the acute phase of infection is common [172]. Up to 46% of patients report fatigue lasting weeks to months post-COVID-19 infection [173]. The degree of fatigue can be subjective, or it can be objectively quantified as a reduction in muscle strength on physical examination [173]. Fatigue is reported both in its "physical" (loss of energy and feeling of heaviness) and "mental" (a feeling of brain fog). Fatigue is often perceived as more intense and persistent in the presence of reduced physical or cognitive activity [174], and complete anamnestic evaluation is crucial to clarify the nature of the symptoms, mechanisms of onset, and impact in patient's quality of life. Cardio-respiratory physical examination with laboratory tests with the values of hemoglobin, glycemia, C-reactive protein, troponin, D-dimer and BNP, and arterial oxygen saturation are of crucial importance. ECG and echocardiography represent the first-level tests for cardiovascular assessment. Chest X-ray and spirometry, on the other hand, represent the first step in analyzing the respiratory system. Cardiopulmonary exercise test (CPET) allows to quantify exercise limitation through the direct measurement of oxygen consumption values (VO_2), thereby allowing to discriminate between a

cardiac or ventilatory or peripheral cause such as dys-autonomic deconditioning or muscle inefficiency. Finally, a correct evaluation of the neuro-phycological and cognitive functions is also important, to exclude possible other causes of fatigue such as anxious, depressive syndrome, or post-traumatic stress disorder. Further examinations will be considered based on the findings observed during the diagnostic process.

3. PACS therapy

Since, nowadays, no specific therapy for cardiovascular diseases associated with COVID-19 or PACS (e.g., myocarditis, acute coronary syndrome, pericarditis, Takotsubo syndrome, atrial or ventricular arrhythmias, and heart failure) are available, the standard of care reported by international cardiac guidelines represents the recommended therapeutic strategy for each specific vascular sequela of the PACS. Although current evidence for of long COVID treatment is lacking, many clinical trials on therapy for CV sequelae treatment of long COVID and are currently underway. Moreover, both SARS-Cov2 acute infection specific therapy and vaccinations are opening up promising scenarios in the prevention and treatment of COVID-19 sequelae. In fact, more than 700 studies related to COVID-19 and more than 100 on long term are ongoing (see International Clinical Trials Registry Platform (ICTRP) (who.int) and see Search of: COVID-19—List Results—ClinicalTrials.gov), thereby suggesting the hope for a "new era" in the treatment of this, in many respects, unknown pathology. Studies include a wide range of therapy such as: rehabilitation programs (for the treatment of fatigue, dyspnea, inappropriate tachycardia, POTS, and cognitive decline), immunomodulatory therapies (e.g. steroids, laranilubmab, tocilizumab, atorvastatin, and colchicine), anti-thrombotic (e.g. aspirin), or anti-coagulation (e.g. apixaban). Although a large amount of evidence confirms a lack of benefit of aspirin in reducing mortality among hospitalized [175] and non-hospitalized outpatients [176], promising results were produced in support of anticoagulation [177]. The multiplatform adaptive randomized controlled clinical trial [178] reported an improved survival in moderately ill patients treated with therapeutic dose of heparin, but not in critical illness. In contrast, other studies [179–181] reported no difference in primary outcome measures among patients receiving therapeutic vs. prophylactic dose anticoagulation. Therefore, further research is therefore needed to better understand the long-term benefits of anticoagulation in patients. Although anti-inflammatory drugs such as dexamethasone [182] and tocilizumab [183] or antivirals such as remdesivir [184] represent the most used and effective therapeutic armamentarium in patients with severe COVID-19, whether they are able to prevent cardiovascular sequelae or to reduce the impact of long-COVID-19 after the acute phase is still unclear. In conclusion, nowadays, the most effective way of preventing serious complications from SARS-CoV-2 infection is represented by SARS-Co2 vaccination [185–191]. Early data [192] have recently suggested the possibility that of long COVID symptoms could be alleviated through vaccination. More specifically, of 900 people with long COVID, only 18.7% of patients reported a deterioration on clinical status, while 56.7% of vaccinated showed an overall improvement in clinical sequelae.

Finally, since the acute phase of COVID-19 is complicated by several multisystem sequelae in a vast majority of subjects, rather than a single drug, subjects with PACS need a multidisciplinary approach aimed at managing each single PACS sequela. This multidisciplinary approach, including clinical, cardiological, pneumological, neurological psychological, and physiotherapeutic evaluation, is generally provided

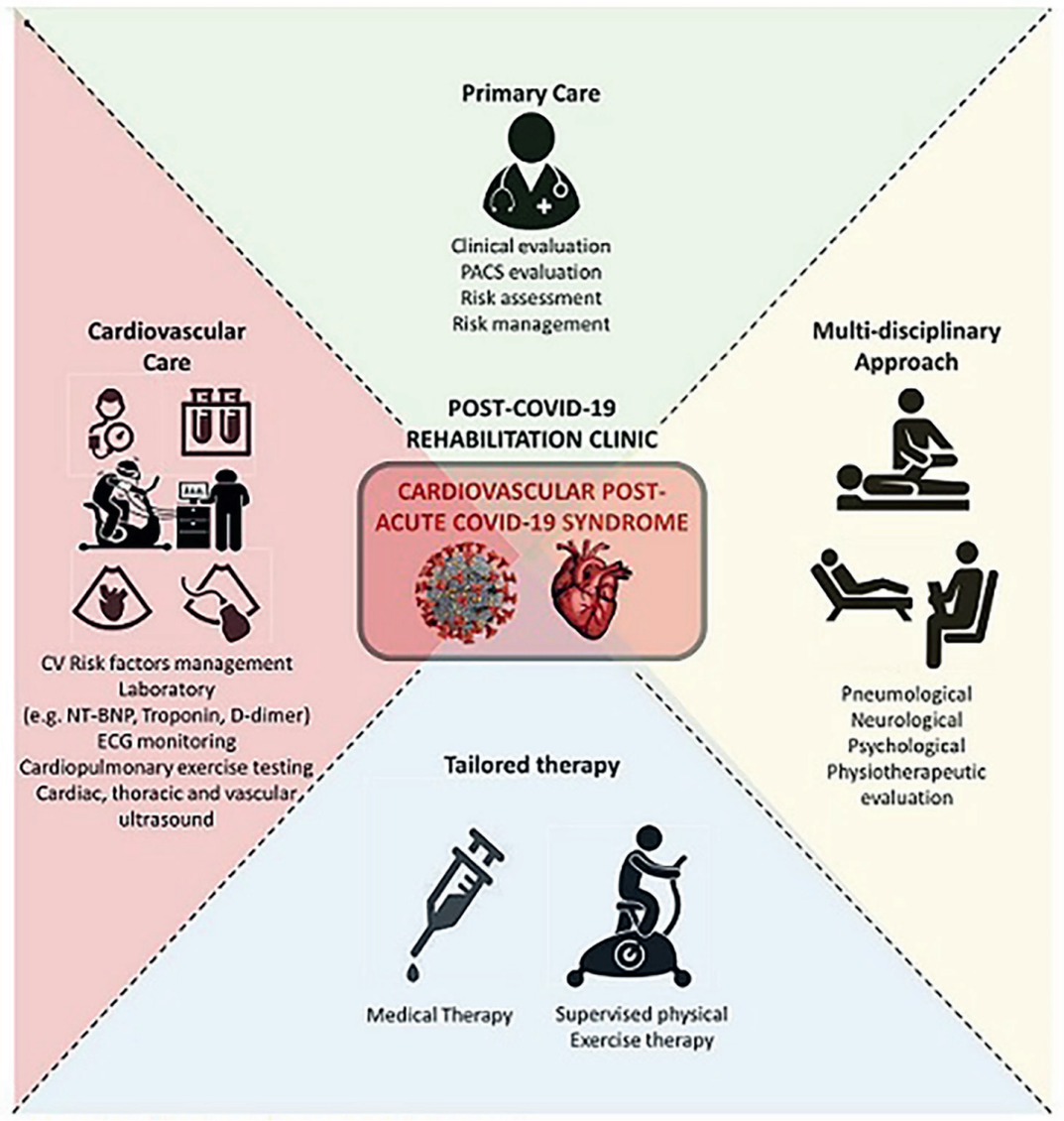

Figure 8.
PACS evaluation and therapy.

by the rehabilitation program of chronic diseases (e.g. cardiac or pulmonary rehabilitation) [193]. For these reasons, on top of the aforementioned therapies, a specific post-COVID-19 rehabilitation approach represents new hope in fighting against the sequelae of PACS (**Figure 8**). In fact, results from early post-COVID-19 rehabilitation registry and trials showed an improvement in dyspnea, anxiety, muscle strength, walking capacity, sit-to-stand performance, and quality of life; on the other hand, results on pulmonary function are still inconsistent [194].

4. Future directions and conclusions

Since many aspects of the PACS remain unclear, further studies will be needed to shed light on the following aspects. First, establish the prevalence SARS-CoV-2-induced CV injury and CV sequelae of PACS. Second, define univocal and universal diagnostic criteria for long-COVID-19, based not only on clinical symptoms but also on specific biomarkers.

Third, identify novel therapeutic solutions or novel use of old drugs to prevent and treat or COVID-19 long-term CV injury. Finally, he long-term prognostic impact of cardiovascular sequelae of SARS-CoV-2 infection in both healthy subjects as well as in patients with preexisting cardiac diseases (e.g. ischemic heart disease, heart failure) is evaluated in order to clarify whether SARS-Cov2 infection or its sequelae beyond the acute phase of COVID-19 may represent a novel risk factor for future cardiovascular disease. In fact, data from the national healthcare databases from the US Department of Veterans Affairs including a large cohort of 153,760 individuals with COVID-19 compared to two sets of control cohorts (5,637,647 contemporary controls and 5,859,411 historical controls) showed that, beyond the first 30 days after infection, individuals with COVID-19 are at increased risk of incident cardiovascular disease spanning several categories, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease [194, 195]. Moreover, these risks and burdens were evident even among individuals who were not hospitalized during the acute phase of the infection and increased in a graded fashion according to the care setting during the acute phase (non-hospitalized, hospitalized, and admitted to intensive care), thereby providing novel evidence of post-COVID-19 cardiovascular prognostic impact. In particular, if these data will be confirmed, the presence of a SARS-Cov2 infection as well as a history of PACS should be considered in the future as a novel parameter in cardiovascular risk estimation beyond traditional cardiovascular risk factors.

Conflict of interest

The authors declare no conflict of interest.

Figures and tables, part of the manuscript, were drawn by the authors and therefore are to be considered an original contribution.

Author details

Claudio Stefano Centorbi[1*], Enrica Garau[1], Leonardo Borsi[2], Valerio Brambilla[2], Lorenzo Brambilla[3] and Davide Lazzeroni[2]

1 Brotzu Hospital, Paediatric Cardiology and Congenital Heart Disease Unit, Cagliari, Italy

2 Fondazione Don Carlo Gnocchi, Parma, Italy

3 IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy

*Address all correspondence to: doc.centorbi@gmail.com

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