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Review

Three Years of COVID-19 Pandemic—Is the Heart Skipping a Beat?

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Abstract: In the context of new therapeutic protocols and vaccines developed in the past 3 years, coronavirus 2019 (COVID-19) continues to exert an important impact on the healthcare systems worldwide. Age and a history of cardiovascular or respiratory diseases remain relevant in terms of prognosis for all COVID-19 patients, independent of the viral strain, by conveying a worse outcome and increased rates of in-hospital mortality. Previous studies reported heterogenous cardiovascular manifestations in COVID-19 patients from acute myocarditis or myopericarditis, acute coronary syndromes, stress cardiomyopathy, de novo arrhythmias to pulmonary embolism, or in some rare cases, endocarditis. In this review, we assessed the potential acute, in-hospital and long-term cardiac complications in patients diagnosed with COVID-19.

Keywords: COVID-19 cardiovascular complications; myocardial injury; long–COVID

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1. Introduction

In the context of new therapeutic protocols and vaccines developed in the past 3 years, coronavirus 2019 (COVID-19) continues to exert an important impact on the healthcare systems worldwide. The clinical spectrum of COVID-19 varies from asymptomatic cases described in almost a quarter of patients to severe forms of pneumonia and acute respiratory distress syndrome requiring intensive care unit (ICU) admission and advanced medical management [1]. Moreover, the variability in COVID-19 clinical scenarios depends as well on the concerned viral strain. The Omicron variant is associated with a lower severity risk and fewer ICU admissions in comparison to Delta variant, emphasizing the additional value of genomic analysis in these patients [2]. Nevertheless, age and a history of cardiovascular or respiratory diseases remain relevant in terms of prognosis for all COVID-19 patients, independent of the viral strain, by conveying a worse outcome and increased rates of in-hospital mortality [3]. One of the most frequent complication described in patients hospitalized with COVID-19 is myocardial injury, which is suggested by an elevation of cardiac biomarkers, in particular, cardiac troponinsand is associated with increased morbidity and mortality [4–6]. However, initial studies focused, in general, on a single cardiac troponin determination, conducted frequently at admission, without considering its dynamicity, which may be indicative of various types of cardiovascular and non-cardiovascular pathologies [7]. The elevation of cardiac biomarkers in patients with COVID-19 is a reflection of several pathophysiological mechanisms, such as cytokine storm, microangiopathy due to prothrombotic state and endothelial dysfunction or hypoxemia, further leading to the destabilization of previously silent coronary artery diseases or de novo type 2 myocardial infarction and newly onset acute myocarditis, pulmonary embolism, sepsis or acute kidney injury, which are frequently observed in COVID-19-positive, hospitalized patients [8–10]. Hence, understanding the multisystem effects of COVID-19

plays a crucial role in making a proper and timely decision regarding various medical treatment strategies, including the transfer to intensive care units, invasive mechanical ventilation or vasopressor support and the improvement of patients' survival and diminishing the potential long-term consequences.

In a meta-analysis comprising 20 studies, the prevalence of myocardial injury in hospitalized COVID-19 patients was up to 22% with distinctive differences between patients with severe forms of disease compared to non-severe COVID-19 patients (from 10.2% to 69.2% versus from 1% to 9%, respectively) [11]. Moreover, when comparing different viral strains, the lowest rates of mortality, ICU admission and mechanical ventilation were described in patients with myocardial injury and the Omicron variant due to decreased virulence, different medical management methods and the effectiveness of vaccination strategies [12].

Previous studies reported heterogenous acute cardiovascular manifestations predominantly in hospitalized COVID-19 patients, from acute myocarditis or myopericarditis, acute coronary syndromes, stress cardiomyopathy, de novo arrhythmias to pulmonary embolism, or in some rare cases, endocarditis. Furthermore, the presence of a cardiac injury was reported in several follow-up studies. Post-acute cardiovascular [13] complications are considered to be common after viral infections, particularly among patients with cardiovascular risk factors and chronic diseases [14]. In comparison to patients without a history of COVID-19, patients who already experienced an acute COVID-19 infection are at a higher risk of cardiovascular diseases, including de novo arrhythmias, ischemic heart diseases or thromboembolic events at one-year follow-up [15]. On top of that, the same study outlined the burden of cardiovascular diseases in recovered COVID-19 patients without common cardiovascular risk factors, such as arterial hypertension or obesity, who are considered to have a poor cardiovascular risk profile [15].

Although our knowledge on coronavirus has improved since the outbreak in 2019, there are gaps in evidence regarding COVID-19 severity, in-hospital management and outcomes, as well as long-term complications following an acute episode. Therefore, in this review, we assessed the potential acute, in-hospital and long-term cardiac complications among patients diagnosed with COVID-19.

An extensive review of literature derived from research involving human subjects, published in English and indexed in MEDLINE (through PubMed) was conducted (Supplemental Table S1). Key search words were included, but were not limited to the following: COVID-19 myocarditis, COVID-19 myocardial injury, COVID-19 pericarditis, COVID-19 acute coronary syndrome, COVID-19 myocardial infarction, COVID-19 cardiac arrythmias, COVID-19 infective endocarditis, COVID-19 stress-induced cardiomyopathy, COVID-19 takotsubo cardiomyopathy, COVID-19 postural orthostatic tachycardia, COVID-19 chronic fatigue syndrome, long COVID and COVID-19 cardiovascular diseases

2. Acute and Delayed Myocardial Injury

Cardiac injury is common in viral infections, including COVID-19. However, the presented evidence is conflicting whether this is induced by direct viral action or caused by the consequences of several indirect factors from the reactivation of the underlying diseases to an overexaggerated inflammatory response [16]. The presence of microthrombosis induced by COVID-19 outlines the cytotoxic effect of the virus on endothelial cells [16]. Moreover, autopsy studies have rarely described the presence of interstitial macrophages at the level of the myocardium in patients presenting, for example, myocarditis; therefore, a potential direct mechanism cannot be entirely excluded [17]. Nevertheless, the high level of macrophages at the level of myocardium in autopsies performed on patients with COVID-19 pneumonia may be due to the increased inflammatory response with the release of proinflammatory cytokines, which is not a unique characteristic for COVID-19 infections [17]. Importantly, it is well known that angiotensin-converting enzyme 2 plays a central role in the processes of inflammation, oxidative stress, vasoconstriction and fibrosis [18], as well as the affinity of SARS-CoV 2 virus to angiotensin-converting enzyme 2 receptor with the hyperactivation of the renin–angiotensin–aldosterone system,

thereby promoting the inflammation process [19]. The mixed effect of the direct viral effect and the inflammation process with cytokine storm, endothelitis and thrombosis occurring at different stages in the evolution of the disease represent the substrate for cardiac injury [10] Subsequently, some patients recovering from COVID-19 may develop long-term consequences with a variable prevalence at different time points [20]. For example, post-COVID lymphocytic and eosinophilic myocarditis was reported between one and five months following the acute infection, with SARS-CoV-2 ribonucleic acid (RNA) being detected in association with parvovirus B19 DNA [21]. Other studies emphasized subclinical cardiac damage following acute pneumonia, which was translated by the chronic elevation of cardiac biomarkers and asymptomatic changes at the level of myocardium and depicted in cardiac magnetic follow-up exams or via positron emission tomography [22]. Although high levels of cardiorespiratory fitness seem to be protective of severe forms of COVID-19 infection, athletes are susceptible to cardiovascular complications that often remain silent, such as myocarditis or a pre-myocardial injury. Moreover, this population might have an increased arterial stiffness and decreased vascular function. These data raise concern about myocardial inflammation as an additional cause of cardiac injury among athletes [23–27].

3. Myocarditis in COVID-19 Pneumonia

Direct viral injury together with a generalised inflammatory response, diffuse vasculitis and/or cardiotoxic anti-viral therapies are considered to induce COVID-19-related myocarditis [28]. However, its pathogenesis remains a subject of debate. Potential mechanisms associated with the onset of myocarditis are separated, as previously mentioned, into two main categories: direct viral action and its indirect effects [19]. Direct viral invasion has been described in isolated cases of fulminant myocarditis associated with COVID-19, where RNA was present at the level of cardiomyocytes [29]. Fulminant myocarditis, which is characterized by a lymphocytic infiltrate on endomyocardial biopsies, remains an infrequent complication of COVID-19 infections [30]. One of the pathophysiological mechanisms linked to the onset of acute myocarditis among patients with COVID-19 is the viral invasion via the spike protein that connects to angiotensin-converting enzyme 2 receptors expressed by various cells including macrophages, thereby promoting inflammation at this level [4,19]. Moreover, in specific clinical situations where an endomyocardial biopsy was performed to confirm the diagnosis of myocarditis, COVID-19 RNA was identified supporting the theory of direct viral invasion [13,30]. The mortality rate among COVID-19 patients is considered to be less than 1%, with myocarditis being a potential cause of a worse outcome [31,32]. However, the prevalence of acute myocarditis is considered to be low, being considered as an uncommon finding among patients with COVID-19 [33]. A recent study described the occurrence of myocarditis in COVID-19 between 2.4 and 4.1 out of 1000 hospitalized patients, which is in contrast with earlier data where the prevalence was up to 60% based mainly on presumed myocarditis diagnosis without actual established diagnosis criteria [34,35]. A multicentric report including 1047 patients described the myocarditis pattern via cardiac magnetic resonance (CMR) in 7.9% of the patients [36]; however, it was limited by the retrospective nature and variability in the CMR protocols used in various centres, along with the absence of previous CMR examinations prior to COVID-19 to exclude pre-existing abnormalities. Nevertheless, the incidence of myocarditis was 42.3% higher in 2020 than it was in 2019, with an increased risk of 0.146% among patients with COVID-19 versus 0.009% among COVID-19-negative patients, respectively. However, it was not possible to determine causality based on the abovementioned data [33]. In the same report, patients with COVID-19 have a 16 times higher risk of developing myocarditis than patients without COVID-19 do [33]. Additionally, several reports evaluated its prevalence among young competitive athletes with a history of COVID-19 due to the high risk of sudden death in this particular population. In one of the largest studies involving 1597 competitive athletes, 37 (2.3%) patients presented clinical and subclinical characteristics suggestive of myocarditis [37]. Other reports consisting of smaller cohorts described a prevalence of myocarditis associated with a COVID-19 infection in up to 15%

of them [38–41]; however, they were limited by differences in the time of examination following the acute episode of COVID-19 or the protocols used for CMR evaluation. In a recent study focusing on myocardial involvement among COVID-19 patients, the authors concluded that excess scarring described during CMR evaluation is predominantly due to myocardial infarction and microinfarction, emphasizing the prothrombotic state of COVID-19 [42]. Additionally, the same report concluded that the prevalence of myocarditis was low, and the pathogenesis of cardiac troponin elevation in this population remains diverse [42]. Nevertheless, COVID-19-associated myocarditis remains a difficult diagnosis to establish in the context of COVID-19 pneumonia due to the similarity of symptoms; one distinguished characteristic would be the early shock state that accompanies the onset of myocarditis in COVID-19 patients [43].

4. Pericarditis in COVID-19 Pneumonia

Acute pericarditis and cardiac tamponade are considered to be rare manifestations associated with a COVID-19 infection. Importantly, patients with acute myocarditis and pericarditis are at a higher risk of a worse prognosis during the COVID-19 acute episode of pneumonia, including developing acute heart failure, and subsequently, left ventricle dysfunction [44].

A possible cause of acute pericarditis among COVID-19 patients may be the inflammatory response due to an acute injury at the level of pericardial mesothelial cells, with it being, in some cases, associated with pericardial effusion [45]. It is already acknowledged that some cardiotropic viruses (e.g., Influenza and adenoviruses) may cause inflammation at the level of myocardial tissue, overstimulating the local inflammatory response, leading to myopericarditis [46]. In the CAPACITY-COVID registry, the reported overall incidence of cardiovascular events was 11.7% (349 patients out of 3011 patients included), out of which, 0.3% represented acute pericarditis and 0.9% represented myocarditis [47]. Pericardial effusion was described in 4.55% of cases via chest computed tomography performed on hospitalized COVID-19 patients [48]. Following the acute episode, several studies described the presence of pericardial late enhancement with pericardial effusion in up to 40% of the recovered COVID-19 patients [49,50]. The contradictory data are related to the differences in the study populations across the studies, lack of standardized protocols and the retrospective nature of the reported information. Moreover, due to the restrictive measurements taken to avoid the unnecessary exposure of healthcare professionals during the first months of the pandemic, pericardial involvement in COVID-19 patients remained often underdiagnosed [51].

5. Stress-Induced Cardiomyopathy and COVID-19 Pneumonia

During the COVID-19 pandemic, stress cardiomyopathy or Takotsubo syndrome was frequently described in both COVID-19 and non-COVID-19 patients. Takotsubo syndrome onset is triggered by severe emotional stress, which promotes catecholamine excess release [52]. In the context of the COVID-19 pandemic, the mechanisms behind stress cardiomyopathy are multifactorial and complex, including the association between physical and emotional stresses, together with endothelial dysfunction, cytokine storm, excessive inflammation response, coagulopathy disorder and microthrombosis, and induced by the infection itself [53,54]. The stress cardiomyopathy prevalence was 4-5 times higher in COVID-19 pandemic era in comparison to pre-pandemic period [55]. Even though it is reversible, patients with Takotsubo syndrome may develop long-term consequences, leading to the onset of heart failure [54,56].

6. Acute Coronary Syndromes in COVID-19 Pneumonia

The potential mechanisms attributed to COVID-19 pneumonia are diverse, and they include thrombosis due to atherosclerosis plaque rupture, mismatch between oxygen supply and demand, referred to as type II coronary syndromes, and uncontrolled inflammation response, cytokine storm, sepsis induced myocardial injury and endothelial dysfunction [57]

(Figure 1). At the beginning of the pandemic, a peculiar evolution of acute coronary syndrome prevalence was noted.

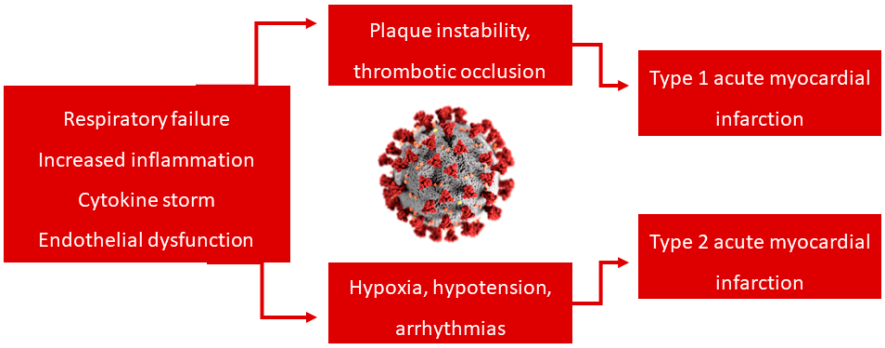

Figure 1. Potential mechanisms of acute coronary syndromes in COVID-19.

A downward trend of acute coronary syndromes prevalence was observed worldwide. In 2020, the Italian Society of Interventional Cardiology reported a reduction of up to 50% of the number of procedures for, e.g., coronarography, angioplasty, transcatheter aortic valve replacement or transcatheter edge-to-edge mitral valve repair, in comparison to that of the pre-pandemic period [58]. Consequently, a delayed presentation to hospital was noticed, with an augmentation of the subacute forms of acute coronary syndromes and related complications, such as malignant arrhythmias, mechanical complications or refractory acute heart failure, conveying a worse prognosis for these patients, with higher mortality and cardiogenic shock rates in comparison to those in the pre-COVID-19 era [57,59,60]. There are several explanations for this trend observed worldwide during the first waves of the COVID-19 pandemic, which are related to the psychological impact of the pandemic on the general population and reluctance to seek medical help, causing delayed presentations to hospitals and the reorganization of medical services focusing on managing the high influx of COVID-19 patients. Unfortunately, in the same context, the year 2020 of the COVID-19 pandemic may be defined as well by an increased incidence of number of out-of-hospital cardiac arrest (OHCA), most of them going unwitnessed or with a late presentation to hospital, and subsequently, with a three-fold increase in the 30-day mortality rates [61–64]. In comparison to 2019, the in-hospital cardiac arrest (IHCA) incidence was also higher in 2020, with a two times higher 30-day mortality rate [63]. Venous thrombotic events, such as deep vein thrombosis (DVT) or pulmonary embolism (PE), were observed more often than arterial thrombosis. These events were associated with a g worse prognosis such as the need for ICU admission, and increased risk of mortality, up to 24.5% [65,66]. A systematic review of 42 studies encompassing 8271 patients described a higher number of venous thrombotic events (21%), whereas the incidence of arterial thromboembolism was much lower (2%); there was a 0.5% rate of myocardial infarction and a 1% rate of ischemic stroke [67]. In addition to the abovementioned mechanisms attributed to the onset of a myocardial injury among those patients, several external factors, such as prolonged immobilization, mechanical ventilation and central venous catheters, led to a worsened prothrombotic state in COVID-19 patients [66–69].

7. Endocarditis and COVID-19 Pneumonia

Concomitant infective endocarditis was rarely reported in patients with COVID-19. As seen in the case of acute coronary syndromes, a downward trend was also described for the number of infective endocarditis cases. There are several case reports on concomitant infective endocarditis and COVID-19, most of them due to Staphylococcus and Enterococcus infections at the level of the aortic valve [70,71]. The explanations for the available reported data on the incidence of infective endocarditis during the COVID-19 pandemic are numerous, from limitations of the number transesophageal echocardiography examinations to the insidious clinical manifestations of both pathologies, where a fever was a central

symptom [72]. Nevertheless, clinicians should be aware that one does not exclude the other one, and proper management should be started as soon as a clinical suspicion exists.

8. Cardiac Arrhythmias and COVID-19 Pneumonia

As assumed, arrhythmic events accompany COVID-19 pneumonia. Several potential mechanisms related to the onset of acute arrhythmias, such as destabilized chronic cardiac diseases, hypoxemia, electrolyte or intravascular volume imbalances, an abnormal immune response, cardiac injury in acute coronary syndromes, acute heart failure or myocarditis and pulmonary or drug-induced hypertension, were previously observed in other viral diseases and also seen in COVID-19 patients [73].

A large meta-analysis comprising 12.499 hospitalized COVID-19 patients showed that 8.7% of patients presented cardiac arrhythmias during the acute infection, with atrial fibrillation being the most prevalent one [74]. There is a higher incidence of atrial fibrillation or atrial flutters in patients hospitalized with COVID-19 in comparison with non-COVID-19 patients, thereby outlining the importance of screening particularly this population [75]. The new onset of atrial fibrillation among hospitalized COVID-19 patients was commonly reported. In a recent study involving more than 30,000 patients, 5.4% of the patients developed de novo atrial fibrillation during the acute episode, leading to doubling the risk of in-hospital death and developing acute cardiovascular events, including the new onset of heart failure [76]. Hence, the presence of cardiac arrhythmias, especially atrial fibrillation, is associated with a worse outcome and potential long-term consequences.

An important aspect to be considered is the fact that at the beginning of pandemic, one of the initial therapies considered for COVID-19 was hydroxychloroquine with or without concomitant azithromycin and lopinavir/ritonavir, which is known to induce QT prolongation, leading to Torsade des Pointes and sudden cardiac death [77]. To support this, a study showed that 20% of patients treated with hydroxychloroquine with or without concomitant azithromycin developed QT prolongation [78]. With more and more patients recovering from COVID-19 and still being symptomatic, this is a crucial aspect to be considered.

9. Long COVID and Cardiovascular Diseases

There are several definitions for the persistence of symptomatology in COVID-19 survivors; however, most of the follow-up studies define post-acute COVID syndrome as the persistence of symptoms beyond 4 weeks following the acute episode of infection, without any other clinical explanation [79]. Moreover, this can be further separated into different categories based on the duration of the symptoms in subacute or ongoing COVID-19, which is defined between 1 month following the acute episode up to 3 months and chronic COVID-19, which is characterized by ongoing symptoms more than 3 months after the acute infection [79]. This newly described syndrome is characterized by a variety of symptoms, suggesting the multisystemic impact of COVID-19 infection. Follow-up studies reported the presence of Long COVID in more than half of the patients, with the most frequent complaints being shortness of breath, fatigue, chest pain, palpitations, cognitive abnormalities, e.g., brain fog, and sleep disturbances, as well psychological effects, for example, anxiety or depression [79,80]. Six-month chest computed tomography follow-up reports showed abnormalities in more than half of the recovered COVID-19 patients, with abnormalities described even at one-year follow-up [81,82]. The following chest computed tomography findings were often detailed in the COVID-19 follow-up studies: lung fibrosis, consolidation and reticulation, or in some cases, atelectasis [81,83,84].

As cardiovascular diseases remain the leading cause of mortality worldwide, the presence of cardiac events during the acute episode of COVID-19 pneumonia should increase the use of screening for potential long-term cardiac sequels in these patients. As inflammation plays a central and crucial role both in COVID-19 and heart failure, one would correctly assume that there will be a future increase in heart failure prevalence in recovered COVID-19 patients.

To support this, a recent study involving COVID-19 survivors emphasized the augmented risk of developing heart failure after the acute episode of COVID-19 infection. Post-recovery, COVID-19 patients had 69% higher unadjusted hazard of developing heart failure after COVID-19, and this remained significantly as well after adjusting for age, risk factors or race/ethnicity, with it being 45% [85]. The same study reported a higher risk among the younger population that is under 65 years old, following the diagnosis of acute COVID-19 [85]. Subclinical cardiac dysfunction may be one of the underlying mechanisms behind the persistence of symptoms among discharged COVID-19 patients [81]. Recovered patients reported the persistence of symptoms such as chest pain, dyspnoea or palpitations even months after the acute episode [81,86]. Studies focusing on recovered COVID-19 patients reported non-ischemic late gadolinium enhancement patterns via CMR linked to a chronic inflammation state and higher vascular rigidity, which is potentially related to post-acute COVID-19 chronic syndrome or long COVID [87]. The persistence of a cardiac injury after the initial episode may be translated into clinical practice in newly onset or unmasked heart failure, acute coronary syndromes or stroke associated with an increased mortality among recovered COVID-19 patients [87,88]. A recent study evaluated the incidence of cardiovascular events in non-hospitalized COVID-19 patients versus hospitalized patients, highlighting the increased incidence of venous thrombotic events for the first category, with hazard ratio of 2.74, whereas in the latter group of patients, the number of both arterial and venous thrombotic events was heightened, irrespective of age, gender or comorbidities [88,89].

10. Postural Orthostatic Tachycardia Syndrome in COVID-19 Patients

Another complex disorder frequently observed among patients recovering from viral diseases is postural orthostatic tachycardia syndrome. Postural orthostatic tachycardia syndrome is characterized by excessive tachycardia in orthostatism, usually an increase of 30 beats per minute of the resting heart frequency or a heart rate of more than 120 beats per minute in the first ten minutes of standing or in a head-up tilt test and generally without having orthostatic hypotension, with it being accompanied by several symptoms such as headaches, bloating, sleep disorders, fatigue and palpitations [90].

Recent studies described the incidence of postural orthostatic tachycardia syndrome in up to 14% of recovered COVID-19 patients and up to 61% of patients who presented with symptoms such as fatigue, palpitations, shortness of breath/dyspnoea, hypotension intolerance or cognitive impairments/brain fog following the acute episode [91].

The mechanisms associated with postural orthostatic tachycardia syndrome have not been fully elucidated, but they overlap the potential pathophysiological mechanisms behind post-acute COVID-19 syndrome (Figure 2). Dysautonomia symptoms were previously described in patients recovering from severe acute respiratory syndrome [92]. The most frequent symptoms observed among these patients were exercise intolerance, concentration difficulties, tachycardia, chest discomfort or breathlessness, which are similar to the symptoms seen in patients with long COVID [91,92]. Both syndromes are presumably characterized by the presence of chronic inflammation, potential myocardial injury, autoimmunity mechanisms against adrenergic and muscarinic receptors, hyperadrenergic states in the context of stress and anxiety, hypovolemia and deconditioning after the acute COVID-19 infection, which are being translated into clinical practice in a diverse and contradictory symptomatology with a significant impact on the quality of life of those patients [91]. Furthermore, this has crucial reverberations on all aspects of the lives of patients, implying additionally difficulties in the medical management from diagnosis criteria to treatment options. It is important to mention that COVID-19 dysautonomia may be reported also in patients with less severe forms of COVID-19 infection; therefore, a direct relation between long COVID-related symptoms, postural orthostatic tachycardia syndrome and the severity of the index episode is difficult to establish [93]. Although the mortality rate and the number of admissions due to COVID-19 have declined significantly due to the vaccination strategy as well due to its natural evolution, an increasing number of patients recovering

from COVID-19 remain symptomatic. A study of 1773 patients reported the persistence of symptoms following the acute episode in up to 76% at the 6 month follow-up, with fatigue, muscle weakness, sleep disturbances and psychological complaints being the most common ones [94], which are symptoms that have frequently been described in patients with postural orthostatic tachycardia syndrome.

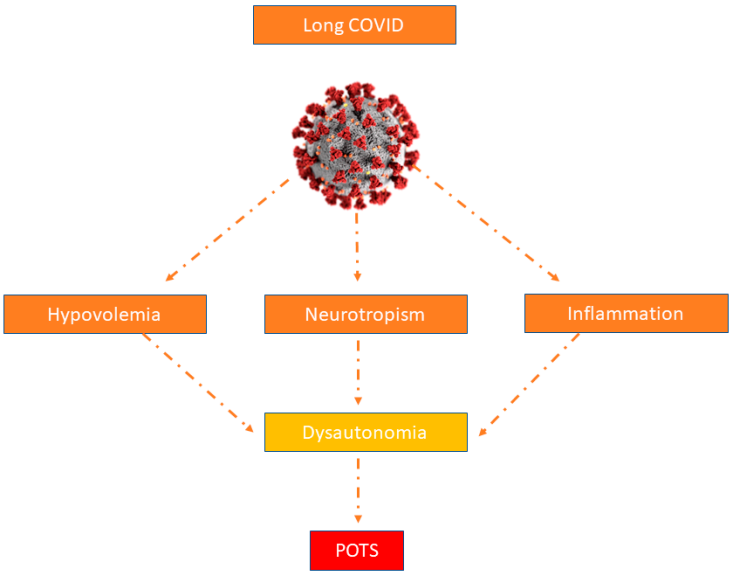

Figure 2. Potential mechanisms associated with postural orthostatic tachycardia syndrome in COVID-19 patients.

11. Chronic Fatigue Syndrome and Long COVID

Viral diseases such as Epstein–Barr virus, enteroviruses or coronaviruses may trigger chronic fatigue syndromes or myalgic encephalomyelitis in recovered patients [95]. According to some studies, the prevalence of chronic fatigue syndrome is considered to be 0.3–0.8% [95]. Similar to postural orthostatic tachycardia syndrome, chronic fatigue syndrome is characterized by orthostatic intolerance, headaches, different degrees of cognitive impairments and sleep disturbances, in addition to chronic fatigue as the name suggests [95]. For many patients, the symptoms are debilitating, affecting their quality of life at all levels. What is more important is the lack of general awareness of chronic fatigue syndrome and specific medical management. Data on chronic fatigue syndrome after COVID-19 acute episode showed a prevalence of 45.2%, with a higher incidence among women than men [96]. In a recent study on the impact of COVID-19 pandemic on the healthcare professionals, 8% of participants reported that there was a direct effect on their work life, whereas 15% of study population reported a negative impact on their social life [84]. Importantly, the abovementioned report consisted of a study population characterized by individuals with mild COVID-19 [96]. Other reports showed no direct link between the severity of COVID-19 and the persistence of symptoms, such as fatigue, dyspnoea or brain fog, following the acute infection [80]. Although there are contradictory data regarding the acute episode of COVID-19 and the risk of developing Long COVID, a general agreement exists regarding the pathophysiology behind it Changes in the immune, cardiovascular, neurological, gastrointestinal and metabolic systems are considered to be the substrates for Long COVID onset in recovered patients [80].

12. Controversial and Unresolved Issues

Despite the recent advances, there are still many unanswered questions regarding COVID-19 and cardiovascular complications.

It is reasonable to believe that treatment should be adapted in view of the evolution of the disease, and also the patients' characteristics. There is, however, still a lack of data

regarding the association of several drugs and the role of the treatment of cardiovascular diseases prior to infection in preventing complications due to COVID-19.

Moreover, there are still some uncertainties regarding vaccination: who should we vaccinate, how often and what type of vaccine should we use, taking into consideration the fact that the severity of the disease changes and patients with high comorbidities are still at risk to lose immunity quickly and are more vulnerable to the disease?

Finally, one of the major questions remains long COVID-19. It is not yet known if the symptoms post-COVID will fully disappear or if they will have life-long sequalae. More research in this field is needed; however, it is still difficult to perform due to high loss to follow-up rates, unvalidated and heterogenous methods and a lack of control groups. Additionally, differential diagnoses between long COVID-related symptoms and other possible diseases remains challenging.

13. Conclusions and Future Perspectives

In this context of newly emerged data on the COVID-19 pandemic, there is still an insufficient amount of information on the mechanisms behind long COVID, and we are still too early in the evolution of the pandemic to see its long-term consequences. Therefore, screening for potential cardiovascular diseases in this specific population would be beneficial to early implement preventive strategies to decrease the burden of cardiovascular diseases worldwide.

Following up with discharged COVID-19 patients is essential for a better understanding and improved management of Long COVID-19 by identifying the patients at risk of developing cardiovascular diseases in order to create and implement targeted medical programs, including individualized treatments with cardiopulmonary rehabilitation for patients with or at risk of developing long COVID-19.

The myocardial implications of COVID-19 are multifactorial, with them being a consequence of a variety of pathophysiological mechanisms from direct viral action to an overexaggerated inflammatory response, with a diversity of clinical scenarios affecting the prognosis and survival of those patients. Long-term cardiac complications have been reported in COVID-19 survivors; therefore, screening for cardiovascular diseases remains the cornerstone for the prompt and individualized medical management of those patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/covid3050053/s1, Table S1: Literature Summary Table.

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