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Review Article

Myocarditis in COVID-19: a focus on the pediatric population

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Abstract: The emergence of the novel SARS-CoV-2 virus in late 2019 introduced new, unpreceded global challenges. Complications arising from COVID-19 widely range from mild to severe and, in some cases, lead to death. The myocardium has proven to be a potential target site for this virus, and has been affected at various levels, resulting in numerous complications, including myocarditis. This article represents a thorough and updated literature review on the clinical manifestations of COVID-19 that pertain to myocarditis, its molecular basis, diagnostic modalities, and treatment approaches, with a special focus on the pediatric population. There definitely is a link between COVID-19 and myocarditis, but the manifestations of this relationship vary from one case to another. At the molecular level, various viral and immunologic factors contribute to the development of myocarditis. Diagnosis, treatment, and outcomes vary as well, but some common trends can be noted. Proper and prompt diagnosis and treatment of SARS-CoV-2-induced myocarditis are crucial. Unfortunately, data in the literature suffers from conspicuous scarcity, especially for the pediatric population; thus, further large-scale clinical studies are required to attain clear and effective guidelines.

Keywords: Myocarditis, COVID-19, SARS-CoV-2, pediatric

Introduction

On January 30, 2020, the World Health Organization (WHO) issued a global emergency declaration in response to the novel coronavirus outbreak in Wuhan, the capital of China's Hubei province. The virus was later identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was determined to be the causative agent of coronavirus disease 2019 (COVID-19). A few months following its emergence, the disease was declared a pandemic on March 11, 2020, with the number of cases surpassing 118,000 in 114 countries [1-4]. Although the majority of cases manifest as upper respiratory symptoms, remarkable extrapulmonary findings with multiorgan involvement have been documented. Unfortunately, the cardiovascular system is at the top of the list of implicated organ systems [5].

Of interest is myocarditis, defined as myocardial inflammation that is mainly manifested by cardiomyocyte necrosis. Endomyocardial biopsy (EMB) is still considered the gold standard for diagnosis (in terms of accuracy), albeit it is rarely performed [6, 7]. Despite the fact that myocarditis can be caused by hypersensitivity reactions to drugs, autoimmune conditions, and other sources, the main cause remains viral [7]. Indeed, with the onset of COVID-19, it was established that myocarditis was a significant complication of the coronavirus. However, due to the possibility of confounding respiratory symptoms of COVID-19 and myocarditis, diagnosis has proven to be difficult at times. Therefore, it has been suggested by Ali et al. that serial troponins and electrocardiograms should be performed on COVID-19 patients to assess for cardiac insults [8].

A considerable amount of data has been fed into the literature that pertains to myocarditis as a consequence of COVID-19. However, the population of particular interest to this paper is the pediatric population. Unfortunately, the

data in the literature pertaining to pediatric myocarditis secondary to SARS-CoV-2 is scarce and largely restricted. Although COVID-19 tends to be mild and generally asymptomatic in the pediatric population, many pediatric patients have proven otherwise. Therefore, in this paper, we provide a comprehensive review of myocarditis as a result of COVID-19, with a special emphasis on the pediatric population. We tackle its molecular basis, various clinical manifestations, diagnostic modalities, and treatment options.

Myocarditis due to SARS-CoV-2

When we analyze the statistics prior to the pandemic, it turns out that 1-10 per 100,000 people were diagnosed with myocarditis annually. This rate typically peaks in healthy, active males who are 18 to 30 years of age. When it comes to myocarditis secondary to the novel SARS-CoV-2 virus, data is mainly derived from case reports, case series and, to a lesser extent, retrospective studies. Furthermore, cardiovascular insults secondary to COVID-19 infection have been widely documented in various forms and severities. Therefore, elevated cardiac biomarkers reflecting myocardial injury are not definitively associated with myocarditis, especially given the lack of a definitive diagnosis via cardiac MRI or a biopsy. These challenges impede the accurate and definitive analysis of COVID-19 related myocarditis epidemiology. However, post-COVID-19, the incidence of myocarditis skyrocketed to reach around 146 cases per 100,000 people [9]. The first recorded case of AFM due to COVID-19 involved a 63-year-old male who had traveled to the Hubei province in Wuhan, China. This case demonstrated that the heart can indeed be a secondary site of infection, and that the manifestation of this damage is not only limited to biomarker changes; it can also be in the form of structural and functional damage. In addition, the immune-related injury seemed to be the primary mechanism of virally induced myocardial injury, which raised questions concerning the specific pathophysiology of this SARS-CoV-2-induced myocarditis [10].

Pathophysiology of SARS-CoV-2-induced myocarditis

Viral penetration into the host cells is accomplished when the SARS-CoV-2 spike glycoprotein is attached to the membrane protein angiotensin-converting enzyme 2 (ACE2) [11]. ACE2 is present on cardiomyocytes, type II pneumocytes, and the ciliated columnar epithelial cells of the respiratory tract. However, to permit binding to ACE2, the spike protein's subunits must first be cleaved at the S1/S2 (priming cleavage) and then at the S2 locations (triggering cleavage) [12]. The priming cleavage transforms the spike glycoprotein into a fusion competent form, which provides better binding ability. The triggering cleavage enables the spike protein to pierce into the host membrane for fusion. The serine protein TMPRSS2 appears to be the mediator of cleavage at the S1/S2 location [12, 13]. SARS-CoV-2 is proposed to induce direct cellular injury after invading the myocytes. Nevertheless, there is no clear evidence to support cardiomyocyte infection by SARS-CoV-2 and subsequent damage. Even in autopsy studies, viral particles couldn't be identified in cardiac myocytes. Pathology findings were only limited to inflammatory cell infiltrates [14].

Besides, it has long been believed that cytokines and chemokines play a significant role in immunity and immunopathology during viral infections. The initial line of defense against viral infections is an immediate and coordinated innate immune response. On the other hand, a dysregulated or hyperinflammatory immune response can result in immunopathology [15]. Specifically, the plasma levels of interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and C-reactive protein (CRP) are markedly elevated in COVID-19 patients, and such an increase in proinflammatory cytokines can lead to multiorgan failure [16]. Thus, this creates a local and systemic hyperinflammatory state that is proposed to result in a myocardial insult.

In addition to that, the SARS-CoV-2 virus plays a role in downregulating the expression of the ACE2 receptor, which consequently increases the quantity of circulating angiotensin II (Ang II), the substrate of ACE2. It has also been shown that Ang II triggers the cleavage and shedding of a soluble form of ACE2 from the membrane via the TNFα-converting enzyme (TACE). A crucial interplay between the renin-angiotensin system (RAS), oxidative stress, and myocarditis is concocted by the concomitant Ang II-stimulated and TACE-mediated loss of myo-

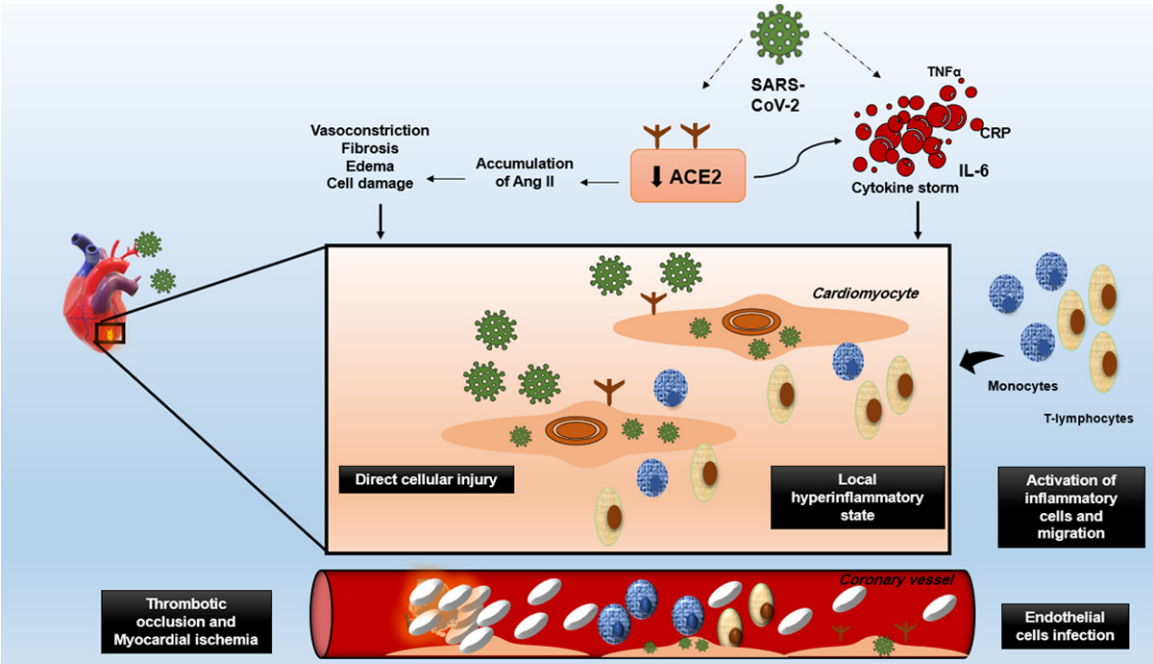

Figure 1. Pathogenesis of COVID-19 related myocarditis. SARS-CoV-2 gains access and infiltrates the cardiomyocytes by binding to ACE2 receptor. Once inside the cell, the viral particles precipitate direct cytotoxic effect on cardiac myocytes. SARS-CoV-2 is also able to induce myocarditis via indirect mechanisms. Inflammatory cells, specifically monocytes and T-lymphocytes, are naturally activated to combat the infection. They migrate to cardiomyocytes where they secrete pro-inflammatory cytokines. Therefore, a local hyperinflammatory state is achieved. Indeed, biopsies revealed infiltration of myocardium with inflammatory cells. In addition, SARS-CoV-2 infects endothelial cells expressing ACE2 receptors, including cells lining the coronary vessels. Through inducing direct cellular injury, the virus triggers inflammatory cascade and leading to thrombus formation and coronary ischemia. At the systemic level, SARS-CoV-2 swarths induction of massive amount of pro-inflammatory cytokines, specifically IL-6, CRP and TNF-α, potentiating the local myocardial inflammation and immune dysfunction. SARS-CoV-2 triggers downregulation of ACE-2 receptors, halting a vital protective mechanism.

cardial ACE2, and this represents a positive feedback loop in the RAS [17, 18].

The extensive expression of ACE2 on the coronary vessels as well as arterial and venal smooth muscle and endothelial cells exacerbates the predisposition to a proinflammatory state, given the aforementioned complications that arise from the virus, especially the cytokine storm that can potentially lead to endothelial dysfunction [16, 19]. **Figure 1** summarizes the potential ways that may lead to SARS-CoV-2-mediated myocarditis.

Myocarditis in the adult population

A few studies with large cohorts have yielded insight on the prevalence of myocarditis induced by the SARS-CoV-2 virus. Boehmer et al. conducted a multifaceted study that included 2,116 COVID-19 patients who developed myocarditis. This study showed that the association between COVID-19 and myocarditis peaked in the younger (<16) and older (>50) age groups, but was the lowest for persons aged 25-39 years. Such a finding can be corroborated by facts pertaining to natural age-related differences in COVID-19 ascertainment. In general, the 25-39 age group is more likely to have a less severe disease, and hence a less likely occurrence of secondary complications such as myocarditis compared to older adults [20]. **Table 1** depicts a comprehensive summary of cardiac-related clinical manifestations in adult patients with myocarditis induced by COVID-19. Studies performed on individual cases or small groups have also provided insight into the topic at hand, and they have been listed in **Table 2**.

Myocarditis in the pediatric population

In a study published in the Morbidity and Mortality Weekly Report from the Centers for Disease Control (CDC), 0.133% of children with

Table 1. Cardiac-related clinical symptoms and measurements of adult patients with COVID-19-induced myocarditis (cohorts)

Reference	Authors	Year	Number of cases	Country	Age (mean)	Male (%)	Physical exam	Myocarditis diagnostics	ECG	Echo	Imaging and Lab	Outcome
[53]	Daniels et al.	2021	37	US	NA	73	Chest pain, palpitations, dyspnea	CMR	NCM (non-compaction cardiomyopathy)	Abnormal, NCM	↑T1, ↑T2, LGE, ↓LVE, ↑troponin	No deaths
[20]	Boehmer et al.	2021	2116	US	54	60	NA	ICD-10-CM	NA	NA	NA	NA
[54]	Huang et al.	2020	26	China	38	38	Precordial chest pain, palpitations, chest distress	CMR	NA	PE	↑T1, ↑T2, LGE, ↑ECV	NA
[55]	Deng et al.	2020	14	China	65	71	Fever, cough, chest pain/tightness, shortness of breath	AHA guideline: triple elevation in troponin with either ECG changes or electrocardiographic changes	ST segment elevation/ST-T changes, tachycardia	Reduced LVEF (<50%), segmental wall motion abnormality, LV wall thickening, PE, TAPSE	↑Troponin	13 deaths
[70]	Laganà et al.	2021	12	Italy	71	42	NA	One criterion from ESC guidelines	Ischemic alteration, QTc prolongation	Diffuse LV hypokinesia	NA (no statistical significance)	3 deaths
[71]	Buckley et al.	2021	35820	US	48	44	NA	ICD-10-CM	NA	NA	NA	NA
[72]	Martinez et al.	2021	3	US	25	NA	NA	CMR	Abnormal	New regional wall motion abnormality; preserved LVEF	NA	No deaths
[73]	Priyadarshni et al.	2022	79	US	NA	NA	NA	ICD-10-CM	NA	NA	NA	NA

Table 2. Cardiac-related clinical symptoms and measurements of adult patients with COVID-19-induced myocarditis (individual cases)

Reference	Authors	Age/Sex/Origin	Past medical history	Physical exam	ECG	Echo	Imaging and Lab	Outcome
[56]	Doyen et al.	69 M, Italian	Hypertension	Fever, cough, dyspnea	LVH, diffuse T-wave inversion	Mild LVH	↑CRP	Recovery
[57]	Hu et al.	37 M, China	NA	Chest pain, dyspnea	ST depression V4-V6	Enlarged heart, LVEF 27%, pericardial effusion	↑troponin, ↑pro-BNP	Recovery
[58]	Kim et al.	21 F, Korean	NA	Fever, cough, dyspnea	Non-specific IV conduction delay, multiple PVCs	Severe LV dysfunction	↑BNP	NA
[59]	Cizgici et al.	78 M, Turkish	Hypertension	Chest pain, dyspnea	Atrial fibrillation, diffuse concave ST elevation	NA	↑troponin, ↑CRP	NA
[60]	Coyle et al.	57 M, US	Hypertension	Fever, cough, dyspnea	Sinus tachycardia	Diffuse hypokinesis with relative apical sparing	↑CRP	Recovery
[61]	Sala et al.	43 F, Italian	Clear	Chest pain, dyspnea	Mild ST-segment elevation in leads V1-V2, reciprocal ST depression in V4-V6	Mild LV systolic dysfunction (LVEF 43%) with inferolateral wall hypokinesis	↑troponin, ↑NT-pro-BNP	Recovery
[62]	Inciardi et al.	53 F, Italian	Clear	Fever, cough, severe fatigue	Diffuse ST elevation, ST depression	Diffuse hypokinesis, LVEF 40%, pericardial effusion	↑troponin, ↑BNP	Recovery
[63]	Oleszak et al.	52 M, USA	Hypertension	Fever, cough, dyspnea, single episode of trace hemoptysis	LV hypertrophy, sinus tachycardia, bi-atrial enlargement, QTc 449	LVEF 10-15%, reduced RV systolic function, global dilatation of all 4 chambers	↑troponin, ↑pro-BNP, ↑CRP	NA

COVID-19 were diagnosed with myocarditis, whereas nearly 0.0033% of children without COVID-19 were diagnosed with myocarditis [21]. While the overall risk seems low, children with COVID-19 had an almost 40 times higher risk of developing myocarditis. When it comes to the pediatric population, no large-cohort studies have been conducted to assess the relationship between myocarditis and COVID-19, although many individual case reports have been published. One such case involves a previously healthy 2-year-old boy who contracted the SARS-CoV-2 virus and developed dilated cardiomyopathy secondary to viral myocarditis. These findings were revealed upon assessment of a myocardial biopsy specimen, where the presence of a viral genome was evident [22]. More information about the COVID-19 post-infective pediatric myocarditis can be revealed by drawing analogies with Kawasaki disease. This is primarily attributed to the well-studied pathophysiology of the systemic arteritis that is observed in this disease. For instance, the ability of neutrophils to form extracellular traps (NETs) to capture pathogens and limit their spread is detected in severe COVID-19 as well as in acute Kawasaki disease. Myocarditis is also known to be a complication that arises from Kawasaki disease [23, 24]. Huge clinical trials are yet to be conducted, though a study of 24 pediatric myocarditis patients by Vucomanovic et al. yielded insight into the distinguishing markers of COVID-19-induced myocarditis, and non-COVID-19-induced myocarditis [5]. One recorded case pertains to the diagnosis of silent myocarditis in a 3-year-old boy due to COVID-19, and its further progression to dilated myocardiopathy and systemic hypertension. Another case concerns the development of acute fulminant myocarditis (AFM) in a 12-year-old girl with dual SARS-CoV-2 and adenovirus infections [25, 26]. **Table 3** depicts the cardiac-related clinical descriptions of pediatric patients with COVID-19 induced myocarditis.

Myocarditis in general: diagnosis

Myocarditis can have various etiologies, which are mainly divided into infectious and non-infectious types. Among the infectious agents, viral etiologies are the most common (adenoviruses, parvoviruses, enteroviruses...). Other microbes contributed significantly to myocarditis, such as bacteria (Staphylococcus spp., Streptococcus spp., Diphtheria spp., Mycoplasma pneumoniae, Rickettsia ricketsii...), fungi (like Aspergillus spp. and Candida spp.), protozoa (like Plasmodium spp. and Toxoplasma spp.), and more. As for the non-infectious causes of myocarditis, they include transplant rejections, allergies, autoreactivity (as seen in giant-cell myocarditis and lymphocytic myocarditis), systemic inflammatory disorders like sarcoidosis, Graves' disease, and inflammatory bowel disease, and so on [27, 28]. Common clinical manifestations that are shared by patients with myocarditis secondary to COVID-19 include: fever, fatigue, chest pain, and shortness of breath. Tachycardia and acute-onset heart failure might ensue upon deterioration [12]. However, they are shared by other cardiac, respiratory, and gastrointestinal illnesses [29]. In terms of chronicity, two major types of myocarditis can be distinguished upon diagnosis: AFM and chronic persistent myocarditis. The former involves a sudden and severe inflammation of the heart that is manifested in ventricular dysfunction, myocyte necrosis and edema, and cardiogenic shock [12, 30]. As for chronic myocarditis, it is defined as an ongoing inflammatory process with secondary fibrosis. Unlike the fulminant one, the chronic form doesn't include myocyte necrosis [31]. To accurately diagnose SARS-CoV-2-induced myocarditis and its specific subtype, the benchmark is EMB [7]. In the clinical setting, however, there are no sensitive or specific non-invasive methods that can definitely ascertain the diagnosis of myocarditis [32]. However, many diagnostic methods can guide this diagnosis. Below is a discussion of the currently employed diagnostic methods.

Endomyocardial biopsy

The importance of EMB arises in its ability to identify the underlying etiology and type of inflammation (sarcoidosis, giant cell, eosinophilic...). This is especially important as each type of inflammation necessitates a specific treatment. Both the American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend EMB as the definitive diagnostic tool for myocarditis. However, EBM still requires a high level of expertise. Studies have shown that when EMB is performed by an experienced operator, it has a complication rate of less than 1% [12, 33, 34].

Table 3. Cardiac related clinical symptoms and measurements of pediatric patients with COVID-19-induced myocarditis

Reference	Authors/Country	Number of cases	Age/Sex	Physical exam	ECG	Echo	Imaging and Lab	Outcome
[74]	Gnecchi et al., Italy	1	16 M	Chest pain, fever	Inferolateral ST-segment elevation	Hypokinesia of the inferior and inferolateral segments of the left ventricle, with a preserved ejection fraction of 52%	↑troponin, ↑CRP	Recovery
[22]	Kesici et al., Turkey	1	2 M	Respiratory distress with filiform pulse, lethargy	NA	Severe LV failure	↑troponin	Death
[75]	Giacomet et al., Italy	1	2 mo. F	Fever, nonbloody diarrhea, 2 episodes of vomiting	Sinus tachycardia	Hypokinesia of the inferior LV wall and the inferior interventricular septum, mild LV dysfunction	↑troponin, ↑pro-BNP, ↑IL-6	Recovery
[25]	Malakan Rad and Momtazmanesh, Iran	1	3 M	Fever, cough	T-wave inversion in left precordial leads	Severely diminished LV systolic function in favor of dilated cardiomyopathy with an ejection fraction of 26%, significant LV enlargement	↑NT-pro-BNP	NA
[26]	Lara et al., US	1	12 F	Fatigue, fever, diffuse abdominal pain, nausea, hypothermia, bradycardia	Complete heart block with atrial rate of 150 bpm and ventricular escape rate of 43 bpm	Severely diminished LV systolic function with an ejection fraction of 27%	↑troponin	Recovery
[76]	Buitrago et al., US	1	12 F	Headache, neck pain, lethargy, nausea, diarrhea, febrile	ST-segment elevations in the inferior leads, II, III, and aVF	Reduced left ventricular systolic function	↑troponin, ↑CRP	Recovery
[77]	Aeschlimann et al., France	20	10 (65% males)	Fever, dyspnea, chest pain, gastrointestinal and respiratory symptoms	No specific results for myocarditis group	LVEF<55% for most of the patients, pericardial effusion	↑NT-pro-BNP, ↑pro-BNP, ↑CRP	NA
[5]	Guner Ozenen et al., Turkey	6	50 mo. (50% males)	Fever, dyspnea, tachypnea, irritability, tachycardia, hypotension, fatigue, abdominal pain	Sinus tachycardia, QTc prolongation	LV systolic dysfunction, LV dilation, left coronary artery ectasia	↑troponin, ↑CRP	NA

Cardiac magnetic resonance imaging

An alternative to the EMB is cardiac magnetic resonance imaging (CMRI). CMRI relies on radiofrequency pulses accompanied by a strong magnetic field. Since no high-energy radiation is applied, CMRI is not known to have any genetic or carcinogenic effects [35]. In addition, it is superior to EMB when it comes to allograft rejection of heart tissue, as it can evaluate the entirety of the myocardium and detect any signs of inflammation. This information can be combined with other parameters such as chamber size, wall thickness, and others to reach a conclusion regarding the suggested etiology. This technique is non-invasive and has been previously used to detect edema and injury in inflammatory conditions like takotsubo cardiomyopathy, acute myocardial infarction, and viral myocarditis [36, 37].

Electrocardiograms

Electrocardiograms (ECGs) are widely used as initial screening tools for diagnosing myocarditis [38]. Despite their low sensitivity and specificity, some ECG changes are more suggestive of myocarditis than others. For instance, although ST segment depression can be observed, ST elevation is the most frequent ST alteration observed in acute myocarditis. ST-T segment elevation in myocarditis is typically concave, as opposed to convex as in the case of myocardial ischemia [33, 39]. In addition, abnormal ECG in viral myocarditis can also feature QT prolongation, premature ventricular complexes, bradyarrhythmia with advanced atrioventricular nodal block, and other signs [12].

Echocardiography

The AHA, ESC, and the American College of Cardiology (ACC) recommend that all patients with suspected myocarditis should undergo a transthoracic echocardiography (TTE) as an initial diagnostic method. Echocardiography carries the advantage that it is a safe, widely available, and non-invasive method [40]. However, since echocardiography investigates chamber sizes, wall thicknesses, and systolic and diastolic functions, it cannot provide direct evidence of myocarditis, and therefore cannot serve as a final diagnostic tool on its own [38]. Advanced echocardiographic tools like speckle tracking echocardiography, tissue Doppler imaging, contrast echocardiography, and three-dimensional TTE can detect subtle abnormalities in ventricular function that can aid in diagnosing viral myocarditis [40].

Treatment of myocarditis

Management of cardiac conditions tends to be based on randomized controlled trials (RCTs). However, myocarditis is not as common as other cardiac conditions, and hence it is difficult to perform trials when it comes to myocarditis. With that being said, several treatment options are available, with varying efficacy. Predominantly, the general principles of treatment apply, meaning that the initial administration of beta-blockers, angiotensin-converting enzyme inhibitors, spironolactone, and loop diuretics is suitable. The cytokine storm that is seen in COVID-19-induced myocarditis is usually mitigated via tocilizumab and interferons. In addition, extracorporeal membrane oxygenation implantation is sometimes needed. Sometimes, in cases of AFM where the left ventricular ejection fraction (LVEF) persistently remains less than 35%, heart transplantation becomes one of the only options left [7, 41, 42]. In the pediatric population, the treatment for acute myocarditis typically consists of supportive therapy, which includes mechanical circulatory support, supplemental oxygen, and fluid restriction [43]. Furthermore, immunosuppressive agents and immunoglobulin (antiviral) therapy have served as potential contenders for the treatment of myocarditis. However, we should keep in mind that the efficacy of therapeutic strategies is not confirmed by clinical trials, and so more trials should be carried out [44].

Immunosuppression

Although immunosuppressive therapy is widely used in myocarditis, more large-scale RCTs are still required to definitively prove its efficacy. Indeed, some RCTs and meta-analyses converge on the concept that immunosuppression treatment can significantly improve LVEF, and possibly reduce LVEDD in myocarditis patients. However, it is still unclear how immunosuppression is correlated with the rate of death and the need for heart transplantation. Interestingly, some evidence has risen in favor of this treatment in the pediatric population specifically, where reductions in the previously mentioned

rates have been recorded [45, 46]. In one study, a significant cure rate was established after immunosuppression with steroid treatment 3 months after the onset of myocarditis, when compared to the conventional therapy group [47]. Nevertheless, studies carried out on corticosteroids, which constitute a crucial component of immunosuppressive therapy, focused on patients with more chronic disease, making the adult affected population heavily studied [4].

Immunoglobulin therapy

Intravenous immunoglobulins (IVIGs) can serve as anti-inflammatory and antiviral agents. In fact, some studies have shown that they can play a role in treating AFM. However, not enough RCTs of antiviral therapy are able to prove that viruses are indeed the therapeutic targets in acute myocarditis [48, 49]. As for the efficacy of this treatment modality, it has been shown to improve the recovery of LVEF (when compared to conventional therapy), and in one trial, AFM patients who received IVIG therapy had better survival rates during follow-up [50]. As per the pediatric population, there were mixed reviews on whether immunoglobulin therapy was an ideal treatment, and it was deemed not associated with better survival chances by one meta-analysis that utilized the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system [51]. Even though IVIG has anti-inflammatory, antiviral, and immunomodulatory effects and is generally regarded as safe by pediatricians, it is not assumed to be immunosuppressive.

Discussion

The COVID-19 pandemic generated several complications that impeded almost every aspect of our daily lives. Therefore, carefully discovering the viral agent's outreach and examining these complications is inevitably a must. In this paper, we present the existing evidence that links the SARS-Cov-2 virus with myocarditis.

It is now generally accepted that SARS-CoV-2 utilizes the ACE-2 receptor to gain intracellular access. Since the ACE2 receptors are commonly associated with the renin-angiotensin-aldosterone system and several cardiovascular conditions and disorders (most notably hypertension), it comes as no surprise that myocarditis can indeed be a consequence of this supposedly respiratory virus [52]. Both pediatric and adult populations are susceptible to this condition. However, the literature that tackles the pediatric population remains scarce and limited, especially since trials involving this group are much tougher to conduct due to stringent ethical issues, a dearth of funding, and so forth.

Thus, closely investigating evidence from the adult literature is crucial. Indeed, large cohort studies, as well as case studies, have been conducted on adults, and they have yielded noteworthy results. Clinical presentation, for instance, seems to be fairly non-specific but similar between the studies compiled, with fever, cough, chest pain, and dyspnea being regularly used words [20, 53-63]. Consequently, clinical assessment alone cannot be used to diagnose myocarditis. Other diagnostic modalities are crucial, including CMRI, ECG, and echocardiography. Each has its advantages and disadvantages, and when combined, they can yield more accurate results. For instance, when it comes to ECG, both ST elevation and depression have been noted, and this segment in particular has been used to detect several cardiovascular maladies [64]. Moving on to echocardiography, LV systolic function is a very crucial parameter for a multitude of indications, which, alongside assessing myocarditis, include the assessment of ventricular arrhythmias, congenital heart disease, valvular disorders, and other cardiac issues [65]. Additionally, several biomarkers are used to evaluate SARS-CoV-2-induced myocarditis, and they include, but are not limited to, troponin, CRP, and brain natriuretic peptide (BNP). Troponin levels are crucial, and of note is the fact that cardiac troponin I differs from skeletal troponin I, as it has an additional 32-amino acid sequence attached to its N-terminus. Its increasing levels seem highly correlated with myocarditis, as is clearly seen in **Tables 1** and **2**, and no case features its decrease post-myocarditis [66]. Similarly, levels of CRP have been noted to increase post-myocarditis, and it seems that this protein was previously correlated with acute myocarditis. Besides, it can serve as a tool that can predict LV damage and dysfunction in myocarditis patients [67]. Similarly, elevation of BNP is also associated with hemodynamical stress caused

by contractility abnormalities, but this finding was specific to perimyocarditis [68].

When it comes to medical management, there are conventional and non-conventional approaches. Conventional methods include the administration of beta-blockers, ACE inhibitors, and angiotensin receptor blockers to help lower blood pressure, impede arrythmias, and remodel the heart muscle post-myocarditis. Diuretics target the aftermath of myocarditis by lowering the bodily fluid congestion that takes place after the weakening of the heart muscle [69]. The non-conventional methods discussed in this paper are immunosuppression and antiviral treatments (using immunoglobulins). They have both shown a certain degree of effectiveness when it comes to survival and other health criteria, especially in the pediatric population. However, digging further is a must to learn the true potential of these treatments and whether they might be modified to become even more potent.

When it comes to the pediatric population, clinicians should have high suspicion of COVID-19 induced myocarditis whenever the patient presents with dyspnea, cough, third-spacing, and fever. An initial point of care evaluation should be performed by ultrasound to grossly assess the cardiac function. An EKG should be obtained simultaneously. This must be followed by a thorough echocardiographic assessment when the patient is stabilized. Furthermore, with the slightest suspicion, laboratory findings should include cardiac serum markers, such as troponin and pro-BNP. Further advanced imaging with cardiac MRI must be considered in all patients with high suspicion of myocarditis, although it might be difficult to obtain in clinically unstable patients. Although EMB remains the gold-standard of diagnosis, it is rarely performed in the pediatric population. Rapid and meticulous intervention should be started whenever myocarditis is suspected. Medical management starts with supportive care that includes careful fluid resuscitation if needed, diuretics, oxygen therapy, and ionotropic support. The use of anti-inflammatory and anti-viral therapy has not been included in a clear guideline for the pediatric population. However, based on the severity of the patient's condition, steroids and intravenous immunoglobulins can be considered.

A vital aspect when discussing myocarditis induced by the COVID-19 disease is determining the outcomes, several of which have been previously discussed (troponin levels, LVEF, and so forth). Many outcomes are listed for individual patients (from both the adult and pediatric population), but generalized statistics pertaining to the outcomes of COVID-19-induced myocarditis are yet to be published. The general outcomes of the disease ranged from death to full recovery, and they are listed in **Tables 1**-**3**. However, more research, especially on large cohorts, has to be done to be able to draw patterns between myocarditis induced by the SARS-CoV-2 virus and the outcomes resulting from it.

Conclusion

The development of myocarditis post-infection by the SARS-CoV-2 virus incurs additional burdens on the patients. It is the responsibility of multidisciplinary medical teams to lessen these burdens. This entails proper diagnosis and management. As discussed previously, data pertaining to COVID-19 induced myocarditis is limited, especially in the pediatric population. Ultimately, we argue that more trials, especially ones involving large numbers of patients, need to be conducted to provide a scientific basis for future guidelines. It is of utmost importance to do so for both the adult and the pediatric populations, especially because of the paucity of trials involving the pediatric one. The data should then help in establishing appropriate plans to treat the patients and prevent the potentially negative outcomes resulting from COVID-19-induced myocarditis.

Disclosure of conflict of interest

None.

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References

[1] Sharma A, Ahmad Farouk I and Lal SK. COVID-19: a review on the novel coronavirus dis-

ease evolution, transmission, detection, control and prevention. Viruses 2021; 13: 202.
[2] Organization WH. International health regulations emergency committee on novel coronavirus in China. 2020 30 January, 2020 [cited 2022 December 12]; Available from: https://www.who.int/news-room/events/detail/2020/01/30/default-calendar/international-health-regulations-emergency-committee-on-novel-coronavirus-in-china.
[3] Al Maqbali M, Al Badi K, Al Sinani M, Madkhali N and Dickens GL. Clinical features of COVID-19 patients in the first year of pandemic: a systematic review and meta-analysis. Biol Res Nurs 2022; 24: 172-185.
[4] Law YM, Lal AK, Chen S, Čiháková D, Cooper LT Jr, Deshpande S, Godown J, Grosse-Wortmann L, Robinson JD and Towbin JA; American Heart Association Pediatric Heart Failure and Transplantation Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young and Stroke Council. Diagnosis and management of myocarditis in children: a scientific statement from the American Heart Association. Circulation 2021; 144: e123-e135.
[5] Guner Ozenen G, Akaslan Kara A, Kiymet E, Boncuoglu E, Sahinkaya S, Cem E, Yilmaz Celebi M, Kacar P, Gulderen M, Uras M, Yılmazer MM, Murat M, Mese T, Agin H, Bayram N and Devrim İ. The evaluation of troponin I levels and myocarditis in children with COVID-19: a pediatric single-center experience. Pediatr Cardiol 2023; 44: 873-881.
[6] Vukomanovic VA, Krasic S, Prijic S, Ninic S, Minic P, Petrovic G and Nesic D. Differences between pediatric acute myocarditis related and unrelated to SARS-CoV-2. Pediatr Infect Dis J 2021; 40: e173-e178.
[7] Guglin M and Nallamshetty L. Myocarditis: diagnosis and treatment. Curr Treat Options Cardiovasc Med 2012; 14: 637-651.
[8] Ali M, Shiwani HA, Elfaki MY, Hamid M, Pharithi R, Kamgang R, Egom CB, Oyono JLE and Egom EE-A. COVID-19 and myocarditis: a review of literature. Egypt Heart J 2022; 74: 23.
[9] Beaumont. Myocarditis risk associated with COVID-19 infection. 2022 February 23, 2022 [cited 2022 December 10]; Available from: https://www.beaumont.org/health-wellness/blogs/myocarditis-risk-associated-with-covid-19-infection.
[10] Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, Wang LF, Gao H, Wang Y and Dong CF. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection 2020; 48: 773-777.
[11] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C and Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271-280, e278.
[12] Siripanthong B, Nazarian S, Muser D, Deo R, Santangeli P, Khanji MY, Cooper LT Jr and Chahal CAA. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm 2020; 17: 1463-1471.
[13] Tang T, Jaimes JA, Bidon MK, Straus MR, Daniel S and Whittaker GR. Proteolytic activation of SARS-CoV-2 spike at the S1/S2 boundary: potential role of proteases beyond furin. ACS Infect Dis 2021; 7: 264-272.
[14] Basso C, Leone O, Rizzo S, De Gaspari M, Van Der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ and Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. Eur Heart J 2020; 41: 3827-3835.
[15] Channappanavar R and Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Seminars in Immunopathology. 2017. Springer.
[16] Abi Nassif T, Fakhri G, Younis NK, Zareef R, Al Amin F, Bitar F and Arabi M. Cardiac manifestations in COVID-19 patients: a focus on the pediatric population. Can J Infect Dis Med Microbiol 2021; 2021: 5518979.
[17] Mehrabadi ME, Hemmati R, Tashakor A, Homaei A, Yousefzadeh M, Hemati K and Hosseinkhani S. Induced dysregulation of ACE2 by SARS-CoV-2 plays a key role in COVID-19 severity. Biomed Pharmacother 2021; 137: 111363.
[18] Patel VB, Clarke N, Wang Z, Fan D, Parajuli N, Basu R, Putko B, Kassiri Z, Turner AJ and Oudit GY. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. J Mol Cell Cardiol 2014; 66: 167-176.
[19] Boisrame-Helms J, Kremer H, Schini-Kerth V and Meziani F. Endothelial dysfunction in sepsis. Curr Vasc Pharmacol 2013; 11: 150-160.
[20] Boehmer TK, Kompaniyets L, Lavery AM, Hsu J, Ko JY, Yusuf H, Romano SD, Gundlapalli AV, Oster ME and Harris AM. Association between COVID-19 and myocarditis using hospital-based administrative data - United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep 2021; 70: 1228.
[21] Price JF. COVID-19 myocarditis in children. 2021.
[22] Kesici S, Aykan HH, Orhan D and Bayrakci B. Fulminant COVID-19-related myocarditis in an infant. Eur Heart J 2020; 41: 3021.

[23] Tissières P and Teboul JL. SARS-CoV-2 post-infective myocarditis: the tip of COVID-19 immune complications? Ann Intensive Care 2020; 10: 98.
[24] Dionne A and Dahdah N. Myocarditis and Kawasaki disease. Int J Rheum Dis 2018; 21: 45-49.
[25] Malakan Rad E and Momtazmanesh S. COVID-19-induced silent myocarditis and newly developed hypertension in a 3-year-old boy. Egypt Heart J 2022; 74: 44.
[26] Lara D, Young T, Del Toro K, Chan V, Ianiro C, Hunt K and Kleinmahon J. Acute fulminant myocarditis in a pediatric patient with COVID-19 infection. Pediatrics 2020; 146: e20201509.
[27] Lampejo T, Durkin SM, Bhatt N and Guttmann O. Acute myocarditis: aetiology, diagnosis and management. Clin Med (Lond) 2021; 21: e505-e510.
[28] Sagar S, Liu PP and Cooper LT Jr. Myocarditis. Lancet 2012; 379: 738-747.
[29] Sozzi FB, Gherbesi E, Faggiano A, Gnan E, Maruccio A, Schiavone M, Iacuzio L and Carugo S. Viral myocarditis: classification, diagnosis, and clinical implications. Front Cardiovasc Med 2022; 9: 908663.
[30] Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, Shah RV, Sims DB, Thiene G and Vardeny O; American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. Circulation 2020; 141: e69-e92.
[31] Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, Friedrich MG, Klingel K, Lehtonen J, Moslehi JJ, Pedrotti P, Rimoldi OE, Schultheiss HP, Tschöpe C, Cooper LT Jr and Camici PG. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. Circ Heart Fail 2020; 13: e007405.
[32] Yendrapalli U, Hassoun A, Zalamea RM and Hritani A. Myocarditis presentation following COVID-19 virus infection versus COVID-19 vaccination. Am J Cardiovasc Dis 2022; 12: 272-277.
[33] Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P and Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013; 34: 2636-2648, 2648a-2648d.
[34] Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, Hill S, Mahrholdt H, Voehringer M, Schieber M, Klingel K, Kandolf R, Böhm M and Sechtem U. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation 2010; 122: 900-909.
[35] Shah S, Chryssos ED and Parker H. Magnetic resonance imaging: a wealth of cardiovascular information. Ochsner J 2009; 9: 266-277.
[36] Butler CR, Savu A, Bakal JA, Toma M, Thompson R, Chow K, Wang H, Kim DH, Mengel M, Haykowsky M, Pearson GJ, Kaul P and Paterson I. Correlation of cardiovascular magnetic resonance imaging findings and endomyocardial biopsy results in patients undergoing screening for heart transplant rejection. J Heart Lung Transplant 2015; 34: 643-650.
[37] Butler CR, Thompson R, Haykowsky M, Toma M and Paterson I. Cardiovascular magnetic resonance in the diagnosis of acute heart transplant rejection: a review. J Cardiovasc Magn Reson 2009; 11: 7.
[38] Fung G, Luo H, Qiu Y, Yang D and McManus B. Myocarditis. Circ Res 2016; 118: 496-514.
[39] Buttà C, Zappia L, Laterra G and Roberto M. Diagnostic and prognostic role of electrocardiogram in acute myocarditis: a comprehensive review. Ann Noninvasive Electrocardiol 2020; 25: e12726.
[40] Adeboye A, Alkhatib D, Butt A, Yedlapati N and Garg N. A review of the role of imaging modalities in the evaluation of viral myocarditis with a special focus on COVID-19-related myocarditis. Diagnostics (Basel) 2022; 12: 549.
[41] Jaiswal V, Sarfraz Z, Sarfraz A, Mukherjee D, Batra N, Hitawala G, Yaqoob S, Patel A, Agarwala P, Ruchika, Sarfraz M, Bano S, Azeem N, Naz S, Jaiswal A, Sharma P and Chaudhary G. COVID-19 infection and myocarditis: a state-of-the-art systematic review. J Prim Care Community Health 2021; 12: 21501327211056800.
[42] Andréoletti L, Lévêque N, Boulagnon C, Brasselet C and Fornes P. Viral causes of human myocarditis. Arch Cardiovasc Dis 2009; 102: 559-568.
[43] Fung RCM, Hon KL and Leung AKC. Acute myocarditis in children: an overview of treatment and recent patents. Recent Pat Inflamm Allergy Drug Discov 2020; 14: 106-116.
[44] Pomiato E, Perrone MA, Palmieri R and Gagliardi MG. Pediatric myocarditis: what have we learnt so far? J Cardiovasc Dev Dis 2022; 9: 143.

[45] Lu C, Qin F, Yan Y, Liu T, Li J and Chen H. Immunosuppressive treatment for myocarditis: a meta-analysis of randomized controlled trials. J Cardiovasc Med (Hagerstown) 2016; 17: 631-637.
[46] He B, Li X and Li D. Immunosuppressive treatment for myocarditis in the pediatric population: a meta-analysis. Front Pediatr 2019; 7: 430.
[47] Aziz KU, Patel N, Sadullah T, Tasneem H, Thawerani H and Talpur S. Acute viral myocarditis: role of immunosuppression: a prospective randomised study. Cardiol Young 2010; 20: 509-515.
[48] Wei X, Fang Y and Hu H. Glucocorticoid and immunoglobulin to treat viral fulminant myocarditis. Eur Heart J 2020; 41: 2122.
[49] Tschöpe C, Cooper LT, Torre-Amione G and Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. Circ Res 2019; 124: 1568-1583.
[50] Huang X, Sun Y, Su G, Li Y and Shuai X. Intravenous immunoglobulin therapy for acute myocarditis in children and adults. Int Heart J 2019; 60: 359-365.
[51] Yen CY, Hung MC, Wong YC, Chang CY, Lai CC and Wu KG. Role of intravenous immunoglobulin therapy in the survival rate of pediatric patients with acute myocarditis: a systematic review and meta-analysis. Sci Rep 2019; 9: 10459.
[52] Shirbhate E, Pandey J, Patel VK, Kamal M, Jawaid T, Gorain B, Kesharwani P and Rajak H. Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. Pharmacol Rep 2021; 73: 1539-1550.
[53] Daniels CJ, Rajpal S, Greenshields JT, Rosenthal GL, Chung EH, Terrin M, Jeudy J, Mattson SE, Law IH, Borchers J, Kovacs R, Kovan J, Rifat SF, Albrecht J, Bento AI, Albers L, Bernhardt D, Day C, Hecht S, Hipskind A, Mjaanes J, Olson D, Rooks YL, Somers EC, Tong MS, Wisinski J, Womack J, Esopenko C, Kratochvil CJ and Rink LD; Big Ten COVID-19 Cardiac Registry Investigators. Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: results from the Big Ten COVID-19 Cardiac Registry. JAMA Cardiol 2021; 6: 1078-1087.
[54] Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, Liu W, Zeng H, Tao Q and Xia L. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. JACC Cardiovasc Imaging 2020; 13: 2330-2339.
[55] Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, Cheng Y, Yan J, Ping H and Zhou Q. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol 2020; 311: 116-121.
[56] Doyen D, Moceri P, Ducreux D and Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. Lancet 2020; 395: 1516.
[57] Hu H, Ma F, Wei X and Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J 2021; 42: 206.
[58] Kim IC, Kim JY, Kim HA and Han S. COVID-19-related myocarditis in a 21-year-old female patient. Eur Heart J 2020; 41: 1859.
[59] Cizgici AY, Zencirkiran Agus H and Yildiz M. COVID-19 myopericarditis: it should be kept in mind in today's conditions. Am J Emerg Med 2020; 38: 1547.e1545-1547.e1546.
[60] Coyle J, Igbinomwanhia E, Sanchez-Nadales A, Danciu S, Chu C and Shah N. A recovered case of COVID-19 myocarditis and ARDS treated with corticosteroids, tocilizumab, and experimental AT-001. JACC Case Rep 2020; 2: 1331-1336.
[61] Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, De Cobelli F, Tresoldi M, Cappelletti AM, Basso C, Godino C and Esposito A. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020; 41: 1861-1862.
[62] Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM and Metra M. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 819-824.
[63] Oleszak F, Maryniak A, Botti E, Abrahim C, Salifu MO, Youssef M, Henglein VL and McFarlane SI. Myocarditis associated with COVID-19. Am J Med Case Rep 2020; 8: 498-502.
[64] Kashou AH, Basit H and Malik A. ST segment. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing LLC.; 2022.
[65] Kosaraju A, Goyal A, Grigorova Y and Makaryus AN. Left ventricular ejection fraction. 2022 May 1, 2022 [cited 2022 December 8]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK459131/.
[66] Fahed AC, Nemer G, Bitar FF, Arnaout S, Abchee AB, Batrawi M, Khalil A, Abou Hassan OK, DePalma SR, McDonough B, Arabi MT, Ware JS, Seidman JG and Seidman CE. Founder mutation in N terminus of cardiac troponin I causes malignant hypertrophic cardiomyopathy. Circ Genom Precis Med 2020; 13: 444-452.

[67] Goitein O, Sabag A, Koperstein R, Hamdan A, Di Segni E, Konen E and Matetzky S. Role of C reactive protein in evaluating the extent of myocardial inflammation in acute myocarditis. J Cardiovasc Magn Reson 2015; 17: P291.
[68] Rdzanek A, Filipiak KJ, Karpiński G, Grabowski M and Opolski G. Exercise urotensin II dynamics in myocardial infarction survivors with and without hypertension. Int J Cardiol 2006; 110: 175-178.
[69] Faris RF, Flather M, Purcell H, Poole-Wilson PA and Coats AJ. WITHDRAWN: diuretics for heart failure. Cochrane Database Syst Rev 2016; 4: CD003838.
[70] Lagana N, Cei M, Evangelista I, Cerutti S, Colombo A, Conte L, Mormina E, Rotiroti G, Versace AG, Porta C, Capra R, Vacirca V, Vitale J, Mazzone A and Mumoli N. Suspected myocarditis in patients with COVID-19: a multicenter case series. Medicine (Baltimore) 2021; 100: e24552.
[71] Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Lane DA and Lip GYH. Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. Eur J Clin Invest 2021; 51: e13679.
[72] Martinez MW, Tucker AM, Bloom OJ, Green G, DiFiori JP, Solomon G, Phelan D, Kim JH, Meeuwisse W, Sills AK, Rowe D, Bogoch II, Smith PT, Baggish AL, Putukian M and Engel DJ. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening. JAMA Cardiol 2021; 6: 745-752.
[73] Priyadarshni S, Westra J, Kuo YF, Baillargeon JG, Khalife W and Raji M. COVID-19 infection and incidence of myocarditis: a multi-site population-based propensity score-matched analysis. Cureus 2022; 14: e21879.
[74] Gnecchi M, Moretti F, Bassi EM, Leonardi S, Totaro R, Perotti L, Zuccaro V, Perlini S, Preda L, Baldanti F, Bruno R and Visconti LO. Myocarditis in a 16-year-old boy positive for SARS-CoV-2. Lancet 2020; 395: e116.
[75] Giacomet V, Manfredini VA, Meraviglia G, Peri CF, Sala A, Longoni E, Gasperetti A, Stracuzzi M, Mannarino S and Zuccotti GV. Acute inflammation and elevated cardiac markers in a two-month-old infant with severe acute respiratory syndrome coronavirus 2 infection presenting with cardiac symptoms. Pediatr Infect Dis J 2020; 39: e149-e151.
[76] Buitrago DH, Munoz J, Finkelstein ER and Mulinari L. A case of fulminant myocarditis due to COVID-19 in an adolescent patient successfully treated with venous arterial ECMO as a bridge to recovery. J Card Surg 2022; 37: 1439-1443.
[77] Aeschlimann FA, Misra N, Hussein T, Panaioli E, Soslow JH, Crum K, Steele JM, Huber S, Marcora S, Brambilla P, Jain S, Navallas M, Giuli V, Rucker B, Angst F, Patel MD, Azarine A, Caro-Dominguez P, Cavaliere A, Di Salvo G, Ferroni F, Agnoletti G, Bonnemains L, Martins D, Boddaert N, Wong J, Pushparajah K and Raimondi F. Myocardial involvement in children with post-COVID multisystem inflammatory syndrome: a cardiovascular magnetic resonance based multicenter international study-the CARDOVID registry. J Cardiovasc Magn Reson 2021; 23: 140.