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Navigating the nexus: Exploring COVID-19's influence on cardiovascular risk in Pediatric population

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Abstract

This literature review navigates the complex interplay between COVID-19 infection and cardiovascular risks in children. Amidst the global pandemic, concerns about potential lasting impacts on youthful heart health have risen. The synthesis of current research examines the pathways through which COVID-19 may contribute to cardiac issues in pediatric patients, probing inflammation, immune responses, and direct viral effects on the cardiovascular system. Additionally, it scrutinizes data on myocarditis and thrombosis occurrences in pediatric COVID-19 cases, delving into risk factors, diagnostic methods, and treatment approaches. By consolidating existing literature, the review provides key insights into the cardiovascular implications of COVID-19 in children, underscoring the necessity for continual research and vigilance in safeguarding the health of young individuals during the ongoing pandemic.

Keywords: Covid-19; Pediatric; Cardiovascular; Inflammation; Immune Response; Viral effects

1. Introduction

The impact of COVID-19 on the cardiovascular health of pediatric patients is a topic that requires attention and further exploration. While the prognosis for COVID-19 infection in general pediatric patients is favorable, there are certain subgroups, such as those with congenital heart disease and poor ventricular function, who are at a higher risk for severe disease [1]. Similar associations have been reported in adults with acute COVID-19, where underlying cardiovascular disease is linked to worse outcomes [1,2]. Therefore, understanding the cardiovascular outcomes in children with COVID-19, especially in low- and middle-income countries, is essential [1,3].

The early months of the pandemic saw a notable decline in physical activity among children with congenital heart disease, mirroring trends observed in other studies of children and adolescents worldwide [1,3,4,5].

This decrease in physical activity has raised concerns about the potential impact on cardiovascular health in pediatric patients with underlying heart conditions during the COVID-19 pandemic [1,2,6,7,8,9]. It highlights the importance of promoting physical activity and maintaining cardiovascular health in this vulnerable population [2,9,10]. Moreover, the scarcity of available data on the effects of COVID-19 in adult congenital heart disease patients emphasizes the need for further research and understanding of the long-term cardiovascular implications of COVID-19 in pediatric patients with congenital heart disease [11]. Therefore, it is crucial to investigate the influence of COVID-19 on cardiovascular risk in the pediatric population, especially among those with underlying heart conditions [1,12]. Given the lack of available

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data and understanding of the long-term cardiovascular implications of COVID-19 in pediatric patients with congenital heart disease, there is an urgent need for comprehensive research and analysis in this area. This research should delve into the impacts of COVID-19 on the cardiovascular system of pediatric patients with congenital heart disease across different demographics and geographic locations [1,13,14,15].

Understanding the potential long-term effects of decreased physical activity and the impact of COVID-19 on the heart health of pediatric patients with congenital heart disease is a critical area of study. Further investigation is required to evaluate the correlation between reduced physical activity and cardiovascular health outcomes in this vulnerable population during the COVID-19 pandemic [1,8,16,17].

Moreover, the potential manifestation of Multisystem Inflammatory Syndrome in Children with cardiorespiratory or isolated cardiovascular symptoms warrants in-depth study. Exploring the unique cardiovascular aspects of COVID-19-related complications in pediatric patients with congenital heart disease is crucial for attaining a comprehensive understanding of the disease's influence on this population [1,2,9,18].

In conclusion, comprehensive research on the cardiovascular risk in the pediatric population, especially among those with underlying heart conditions, is imperative for developing effective strategies to mitigate the impact of COVID-19 on this vulnerable group [1,2,9,10,18,19].

2. Understanding COVID-19 in Pediatric Patients

2.1. Presentation of COVID-19 in children

Children of all ages are affected by the COVID-19 pandemic, which is a mild illness. With COVID-19, nonspecific symptoms like fever and cough are frequently reported as presenting complaints. Normal leukocyte counts and a low incidence of lymphopenia are typically observed in laboratory settings. The main characteristics in children under one-year-old were a high incidence of critical illness and symptoms of vomiting [20].

Despite being a respiratory pathogen, it can also cause hepatocellular damage and gastrointestinal symptoms (such as diarrhea, vomiting, abdominal pain, and nausea), among other extra-pulmonary manifestations. A proposed mechanism of injury is that the gastrointestinal tract, hepatocytes, and cholangiocytes co-express the entry receptor for the causative coronavirus SARS-CoV-2, transmembrane serine protease 2 (TMPRSS2), and the ACE-2 receptor, which facilitates entry into the tissue and causes direct viral tissue damage. These tissues are similar to respiratory mucosa [20,21].

2.2. Long-term effects of COVID-19 on pediatric patients

Systemic manifestations affecting the neurological, gastrointestinal, cardiovascular, otorhinolaryngologic, and ophthalmic systems have been reported, despite the fact that this disease primarily affects the respiratory system [22,23,24]. The majority of COVID-19-related illnesses in children are mild [25]. After contracting COVID-19, younger children and those with pre-existing comorbidities like obesity are more likely to experience a critical illness [25]. The most effective method for comprehending the pathophysiology of COVID-19 diseases and how they relate to clinical findings is through autopsy. A systematic review showed that DAD (diffuse alveolar damage) was discovered in 78.3% of pediatric autopsy cases in the field of lung pathology moreover hepatosplenomegaly, cardiomegaly, pericardial and pleural effusion, heavy soft lung, enlarged kidney, and enlarged brain were all present [22]. Sleep disturbances, anxiety, depression [23, 26], chronic fatigue, and sensory problems are the most reported psychiatric and neurologic symptoms [23]. The COVID-19 lockdown has caused psychological distress [23,26] and brought attention to risk factors like irregular and excessive COVID-19 media exposure, as well as vulnerable groups like those with mental health issues [26]. Most of the time, the only ocular symptoms are conjunctival hyperemia or chemosis, and they are mild. On the other hand, patients infected with SARS-CoV-2 who exhibit severe ocular disorders also show a high viral load and significant systemic pathological changes [24]. Extended COVID is a complex illness that includes multiple organ systems being affected [22,23,24,27], dysautonomia, vascular and clotting abnormalities, and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [27].

2.3. Factors influencing COVID-19 severity in children

In pediatric patients, age and pre-existing comorbidities are the primary risk factors (table 1). [25,28,29]. Research carried out during the initial year of the pandemic revealed that several minor nucleotide polymorphisms, male sex, leukopenia, neutrophilia, advanced age, and specific comorbidities were significant risk factors for the severity of the illness and death following infection [29]. Compared to COVID-19 infection alone, COVID-19 bacteremic co-infection

demonstrated an increased risk of ICU admission, mechanical ventilation, and in-hospital mortality that was unrelated to the SARS-CoV-2 variant [28]. Prior research has identified hospitalization, female sex, and a history of allergies and underlying chronic diseases as risk factors for pediatric PCC post-COVID-19 conditions.[30] A higher frequency of long-term COVID-19 affecting multiple systems and organs was seen in pediatric survivors with MIS multisystem inflammation syndrome [31]. Environmental factors such as pollution, chemical exposures, climate, and built environment have also been linked to complications in COVID-19 management [32]. Since controls have also reported persistent symptoms, it is challenging to determine causation in many post-COVID symptoms. It is still unclear what long-term effects lockdown and social isolation will have on a person's exposure to common allergens and microbes [33].

Table 1 Risk factors and how they relate to the severity and infection of COVID-19 in children

Risk factors for COVID-19 infection and severity	**Correlation**
Age (young children and/or mature teenagers)	• Low or nonexistent pre-existing immunity to help protect against severe lower respiratory illness caused by SARS-CoV-2 • Infancy of the immune system • Reduced chance of wearing face masks and the ensuing high viral load;
Pre-existing comorbidities	• A weakened immune system • Previous organ damage accelerates the spread of COVID-19 • Sustained lower immunity status lowers resistance to viral infection

3. Cardiovascular Risk Factors in Paediatric Population

3.1. Overview of common cardiovascular risk factors in children

Cardiovascular morbidity and mortality rates are escalating in developed countries, due to the obesity epidemic. This concerning trend affects individuals of all ages, including children and young adults. It is crucial to recognize that obesity and body composition significantly impact the development of other cardiovascular risk factors, extending beyond fat mass alone. Body composition can be utilized as an additional determinant for assessing cardiovascular risk. With modern lifestyles contributing to the prevalence of traditional risk factors like hypertension, obesity, dyslipidemia, insulin resistance, and kidney damage in children, there is a heightened risk of premature cardiovascular events in adulthood for this population [34, 35]. Childhood serves as a critical period for the development of cardiovascular disease (CVD). Evidence suggests that factors such as childhood obesity, abnormal blood pressure, dyslipidemia, diabetes, and tobacco use are associated with intermediate CVD markers in young adulthood [3]. Longitudinal studies reveal distinct blood pressure pathways from childhood to young adulthood, indicating the progression toward hypertension [36,37]. Abnormal low-density lipoprotein cholesterol levels can also be observed in childhood among individuals with familial hypercholesterolemia [36,38].

Genetic predisposition and cardiovascular risk factors can initiate a sequence of pathophysiological changes leading to the progression of atherosclerosis [35]. Obesity plays a significant role in this process, as it is associated with endothelial dysfunction, subclinical inflammation, insulin resistance, and the development of atherosclerotic lesions, driven by factors such as adipokine secretion, inflammatory cytokines, and increased serum uric acid levels [35,37].

3.2. Pre-existing conditions and their impact on COVID-19 outcomes

While respiratory symptoms are the primary clinical expression of COVID-19, there is a growing recognition of cardiovascular complications as a major concern in pediatric patients with SARS-CoV-2 infection [39]. Many studies showed that a significant percentage of pediatric severe complications and deaths associated with COVID-19 were attributed to individuals with pre-existing cardiovascular conditions [39,40,41,42,43]. These cardiovascular conditions include congenital heart disease (CHD), long QT syndrome (LQTS), hypertrophic cardiomyopathy (HCM), and more [40].

Congenital heart disease (CHD) affects 1% of the population. Children with CHD face elevated risks of complications from respiratory viral infections, such as influenza and respiratory syncytial virus (RSV) [40,41]. However, data are scarce concerning the complications associated with COVID-19 infection in children with CHD [40,41]. Children diagnosed with congenital heart disease (CHD) exhibited a higher likelihood of experiencing severe complications, both

cardiovascular (such as tachyarrhythmia and conduction abnormalities) and non-cardiovascular (including acute respiratory failure, the need for invasive and non-invasive ventilation, and acute kidney injury). Additionally, the duration of hospitalization was extended for children with CHD when compared to those without the condition [40,41].

Another cardiovascular disease in children is the genetic heart disease (including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, dilated cardiomyopathy, and catecholaminergic polymorphic ventricular tachycardia) that consists of diverse conditions that impact the electrical system (channelopathies) or the heart muscle (cardiomyopathies) [40]. COVID-19 virus can result in a range of serious heart-related complications including cardiomyopathies, arrhythmias, and myocardial dysfunctions [40,44]. Hence, individuals with cardiomyopathies who contract COVID-19 face a significant risk of deteriorating clinical conditions, especially if they have a history of prior heart failure, arrhythmic events, or documented myocardial dysfunction through echocardiography [40].

Moreover, COVID-19 elevates the risk of myocardial injury in individuals with pre-existing cardiovascular conditions, and this, consequently, is a marker associated with higher mortality rates [43].

3.3. Emerging cardiovascular complications related to COVID-19 in pediatric patients

Even though COVID-19 primarily affects the respiratory tract, it can also engage with the cardiovascular system, resulting in myocardial injury and additional cardiovascular issues.[40][44] Cardiovascular problems are strongly linked to COVID-19 infection. They can significantly negatively influence a person's life and health outcomes in the long term by increasing mortality and morbidity rates.[44,45,46] It has been noticed through a cohort study that cardiac injury is more likely to be noticed in males, older patients, and those having more co-morbidities such as diabetes, hypertension…[45], and pre-existing cardiovascular disease patients [40,43] in addition to that, it was obvious that hospitalized patients with severe infections are most vulnerable [43,44].

Children with COVID-19 are more likely to be asymptomatic or mild diseased however they are still at risk of critical illness, especially those with severe COVID-19 infection [47,48]. When children and adolescents suffer acute severe COVID-19 or multisystem inflammatory syndrome, they can experience tachyarrhythmias such as supraventricular tachycardia, ventricular tachycardia, and accelerated junctional rhythm. These tachyarrhythmias are linked to worse clinical outcomes [47]. It was also noticed that those having atria tachyarrhythmias have higher CRP and D-dimer levels compared with patients who don't have them.[45] Other cardiovascular complications seen in pediatric patients with COVID-19 include myocarditis, which is associated with an elevated c-TN level in some patients, and cardiomyocyte necrosis, dysrhythmia, pericarditis, ischemic heart disease, heart failure, and thromboembolism (associated risk up to 71%) [44,45,46].

Another clinical consequence of COVID-19, which is considered indirect, is the cytokine storm involving a high CRP, ferritin, D-dimers, chemokines… and this storm can be due to the direct invasion of the virus damaging the epithelial cells resulting in an exaggerated inflammatory response leading to this release., the result will be cardiac injury [44,45,46,48].

Another complication considering COVID-19 is the coagulopathies. The blood clotting problems associated with COVID-19 are caused by various factors such as hypercoagulability due to inflammation, issues with how blood vessels function, activation of platelets, and decreased clot breakdown [40,45,46]. When adults with COVID-19 are hospitalized, they are more prone to developing venous thromboembolism or deep vein thrombosis, which raises the risk of strokes and other serious outcomes, ultimately leading to higher mortality rates [44,45,46]. This issue may also impact pulmonary vessels, potentially leading to pulmonary hypertension due to pulmonary embolism, although such occurrences are rare in children [40,45,46].

4. Mechanisms Underlying COVID-19-Related Cardiovascular Complications

4.1. Myocarditis and Hypertension due to direct Viral Invasion

Myocarditis, which is inflammation of the heart muscle, can occur due to various causes, including viral infections such as COVID-19[49], where myocarditis impacts a substantial number of individuals globally, particularly among children and young adult males. This disease can lead to serious outcomes such as sudden cardiac death, unexplained dilated cardiomyopathy, and heart failure in these demographic groups [50]. COVID-19 is characterized by a single-stranded RNA structure with a positive charge, enveloped by glycoproteins and numerous spike [S] proteins covered in polysaccharides [49,51,52,53]. The receptor binding domain within the S1 subunit is responsible for binding to

angiotensin-converting enzyme 2 (ACE2) receptors on host cells, enabling vial entry, where ACE2 is abundantly expressed in various tissues including Cardiac tissue (Figure 1) [49,51,53,54].

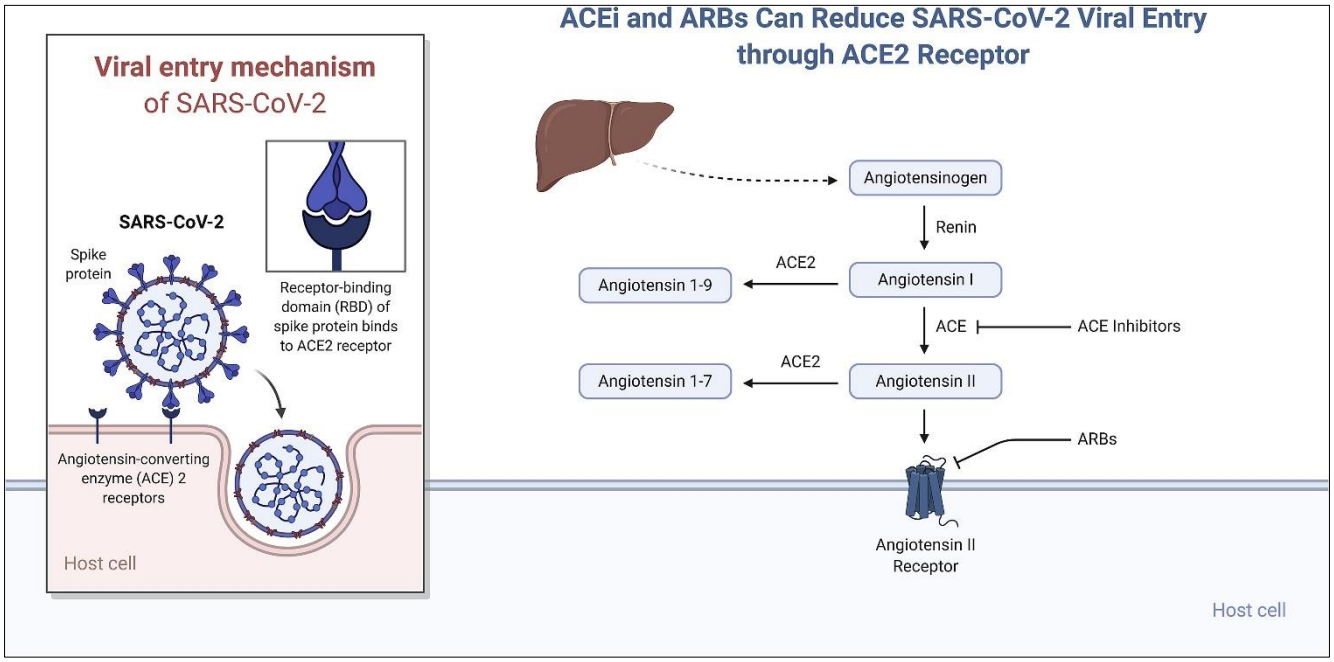

Figure 1 SARS-CoV-2 enters human cells by binding its spike S protein to ACE2 receptors, where ACE2 receptors are part of the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure and Fluid balance in the body. When the virus binds to ACE2 receptors, it can lead to a downregulation of these receptors, reducing their normal function. ACE2 normally acts as a counterbalance to ACE, which promotes vasoconstriction and raises blood pressure. So, the reduced ACE function disrupts the balance in the RAAS. This imbalance can result in an overactive ACE-angiotensin II pathway, leading to vasoconstriction, sodium retention, and high blood pressure [49,52,54]

This was revealed through studies, that there is a potential for ACE2 gene variations, levels of human ACE2 mRNA expression, and variations in human ACE2 protein to impact susceptibility to SARS-CoV-2 and the outcome of COVID-19 disease [55].

Moreover, the acute myocardial damage induced by SARS-CoV-2 in severe COVID-19 cases may be linked to the suppression of ACE2's enzymatic action [55]. In addition, the elevated levels of pro-inflammatory cytokines (PICs) and chemokines like interleukin 1,6,12, and 8, monocyte chemoattractant protein-1 (MCP-1), and interferon-gamma-inducible protein 10 are notably present in both SARS and sever COVID-19 patients [56].

In line with earlier discoveries, it was observed that patients suffering from severe COVID-19 experience notable elevations in cytokines such as IL-2, IL-7, IL-10, GSCF, IP10, MCP-J, MIP1A, and TNF-α, indicative of cytokine storm [53]. Moreover, recent illustrations and reviews showed that viruses are the primary culprits behind myocarditis in children, although the disease can be triggered by numerous other factors [57], on April 27, 2020, the Pediatric Intensive Care Society issued a warning about a rise in the number of cases of a multi-system inflammatory disease accompanied by myocardial damage in children who tested positive for COVID-19, where a case report of a pediatric patient has been reported with isolated acute myocarditis as the sole occurrence of COVID-19 infection [58]. Moreover, recent studies showed that the widespread presence of ACE2 in the coronary vessels, as well as arterial and venous smooth muscle and endothelial cells, intensifies the susceptibility to an inflammatory condition [59], where this is due to the complications that can occur from the virus, particularly the cytokine storm [53,59] that could potentially result in endothelial dysfunction, where the SARS-CoV-2 Spike Protein 1 showed to activate microvascular endothelial cells injury [60,61].

4.2. Blood clotting disorders and their connection to COVID-19

COVID-19 has been linked to an increased risk of blood clotting disorders in various populations [62,63,64]. Studies have indicated that the virus can cause hypercoagulability, which in severe situations can result in disorders including deep vein thrombosis (DVT) and pulmonary embolism (PE) [62,63,64]. This phenomenon is not limited to adults, and

pediatric patients have also exhibited clotting complications associated with COVID-19. Complex and varied mechanisms underlie the connection between blood coagulation disorders and COVID-19 in juvenile patients.[65,66] Even though our knowledge of these processes is still developing, several important factors raise the likelihood of clotting difficulties in people who already have clotting disorders or who have COVID-19.

- Inflammatory Response: COVID-19 causes the body to respond with a strong inflammatory reaction [67]. This inflammatory condition may have a role in the blood clotting pathways being activated [67,68]. This increased inflammatory response may make young patients more vulnerable to clot formation if they already have clotting issues [67,68].
- Endothelial Dysfunction: Endothelial cells that line blood arteries may be negatively damaged by the virus. A prothrombotic state brought on by endothelial dysfunction may encourage the development of blood clots [69]. Children who have underlying coagulation abnormalities may be more susceptible because of their potential impairment in controlling this process [69,70].
- Cytokine Storm and Hypercoagulability: The inflammatory signaling molecules known as cytokines may spike in severe COVID-19 instances, including those in pediatric patients. This hyperinflammatory state may exacerbate a hypercoagulable state, which may facilitate thrombi production [71,72,73].
- Activation of Coagulation Pathways: It has been demonstrated that the virus activates clotting factors and platelets, two elements of the coagulation system [20]. This activation can upset the delicate balance of hemostasis in people who already have clotting problems, resulting in aberrant clot formation [62,74].
- Complement Activation: Severe COVID-19 cases have the potential to activate the complement system, which is an essential component of the immunological response.[75] This activation could increase the likelihood of clotting events and cause endothelial damage [75,76].
- Multisystem Inflammatory Syndrome in Children (MIS-C): Children with COVID-19 may experience MIS-C, a disorder marked by systemic inflammation throughout several organ systems. The inflammatory response triggered by MIS-C has been linked to thrombosis and vascular problems. It has also been linked to clotting problems [77,78].
- Antiphospholipid Antibodies: Antiphospholipid antibodies may develop in some people with severe COVID-19, including children. These antibodies are linked to a higher risk of blood clotting. The existence of these antibodies in juvenile patients with pre-existing coagulation problems may exacerbate the clinical picture. [79,80].

A multidisciplinary approach is essential for the care of pediatric patients with blood clotting problems and COVID-19. Anticoagulant drugs may be considered, and indicators of clotting issues must be closely monitored. Treatments aiming at lowering inflammation and treating clotting difficulties may be used in the setting of MIS-C

4.3. Multisystem Inflammatory Syndrome in Children

Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but severe condition that has been associated with COVID-19 [77]. One prominent component of MIS-C is its effect on children's cardiovascular systems [77,78].

4.3.1. Myocarditis and Cardiac Involvement:

Inflammation of the Heart Muscle: Myocarditis, or inflammation of the heart muscle, is a common symptom of MIS-C. This inflammation can impair the heart's capacity to adequately pump blood, resulting in symptoms such as chest discomfort, tiredness, and irregular cardiac rhythms [81,82].

Cardiac Dysfunction: Children with MIS-C may demonstrate cardiac dysfunction symptoms such as an enlarged heart, decreased heart function, and increased cardiac enzymes [82]. Severe cases may develop into cardiac failure, necessitating immediate medical care [83].

4.3.2. Vascular Involvement and Endothelial Dysfunction:

Endothelial Inflammation: MIS-C can cause inflammation of the vascular endothelium, which lines the blood vessels. Endothelial inflammation may contribute to vascular disorder and damage blood vessel integrity [84].

Increased Clotting Risk: MIS-C is associated with a prothrombotic condition, which is characterized by an increased tendency for blood clot formation. Endothelial dysfunction is a factor in this process, which can lead to thrombotic problems and decreased blood flow [84].

4.3.3. Kawasaki-Like Features:

Identicalities to Kawasaki Disease: Some clinical symptoms of MIS-C are similar to those of Kawasaki illness, another inflammatory syndrome affecting blood vessels, notably the coronary arteries.[30] Both disorders can result in coronary artery aneurysms, which are associated with long-term cardiovascular risks [85].

Coronary Artery Involvement: Coronary artery dilatation or aneurysms have been reported in severe cases of MIS-C [86]. Long-term coronary problems can be minimized with regular monitoring and early management [86,87].

5. Case Studies and Research Findings

5.1. Summary of key research studies exploring COVID-19 and cardiovascular risks in pediatric patients

Severe COVID-19 was significantly associated with both congenital and acquired cardiac conditions. The odds ratio of severe COVID-19 was 9.92 for patients with a previous history of cardiac arrest, 3.07 for patients with cardiogenic shock, 1.91 for patients with cardiopulmonary disease (CPD), and 1.82 for patients with heart failure [88].

Yet, in an article published by the famous American Heart Association (AHA) force, they mentioned MIS-C which is a novel multisystem inflammatory syndrome in children, emerged globally during the COVID-19 pandemic, with cardiac involvement in up to 50% of cases. The incidence of MIS-C among children with COVID-19 infection was 0.032% in the first year of this pandemic [89]. Pulmonary infection can lead to alveolar damage and elevated diffusion of microvessels, potentially facilitating the entry of SARS-CoV-2 into the bloodstream. Given that the heart receives blood from the lungs through the pulmonary circulation, it is conceivable that the heart is a primary site of impact. Various molecular mechanisms involving tissue damage, endothelitis, and thrombosis have been proposed as contributors to this process (Figure 2)[90].

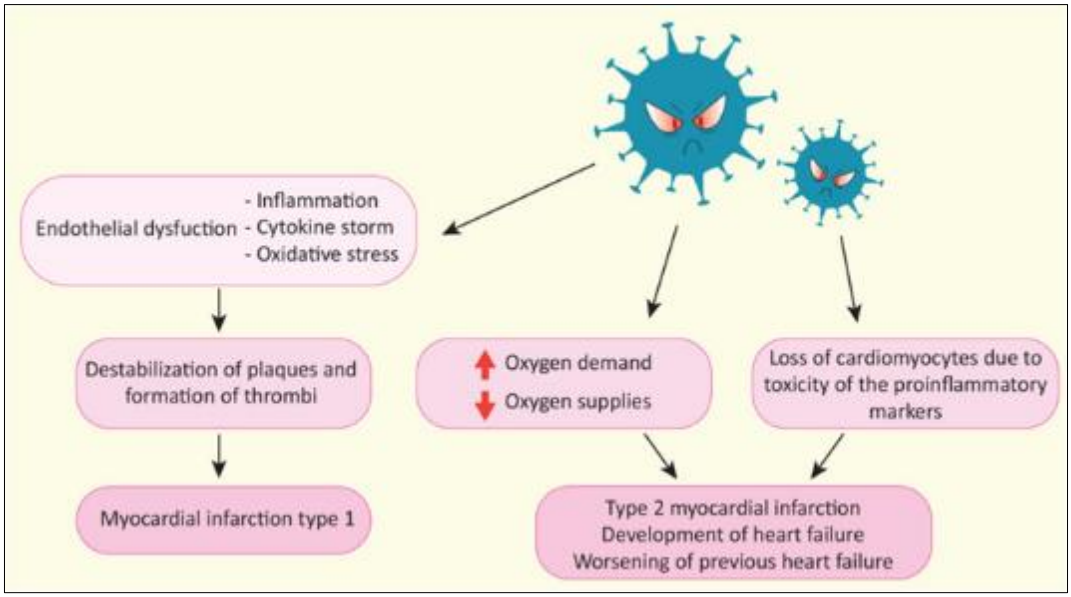

Figure 2 Representing SARS-CoV-2 infection may cause a myocardial infarction, and a visual depiction illustrates the diverse mechanisms through which the virus induces this exacerbating cardiac event. The probable explanation for myocardial injury involves a convergence of multiple deteriorative processes. One of the suggested hypotheses revolves around endothelial dysfunction, initiating sequential events that lead to compromised coagulation, thrombosis, and destabilization of atherosclerotic plaques [90]

In a study conducted on US children and adolescents, a reduced number of COVID-19 patients (19.2%, 111 out of 578) underwent echocardiographic evaluation. Among those that have been assessed, instances of depressed ejection fraction (5.4%, 6 out of 111) and coronary aneurysms (0.9%, 1 out of 111) were uncommon [91].

Critically ill pediatric COVID-19 cases are rare, the disease manifests with diverse clinical presentations in children, emphasizing the importance of considering myocardial injury and cardiovascular issues to prevent the misdiagnosis of severe clinical conditions. Limited data exist for specific pediatric subpopulations, particularly those with underlying

conditions, but certain reports suggest an elevated risk of morbidity and mortality in these groups. Children with preexisting complex cardiovascular conditions may face heightened vulnerability, necessitating vigilant monitoring and follow-up in the event of infection. Rigorous preventive measures, such as frequent handwashing, adherence to social distancing protocols, proper use of masks and personal protective equipment, and the integration of technology, should be prioritized in their management to mitigate the risk of nosocomial infections [92].

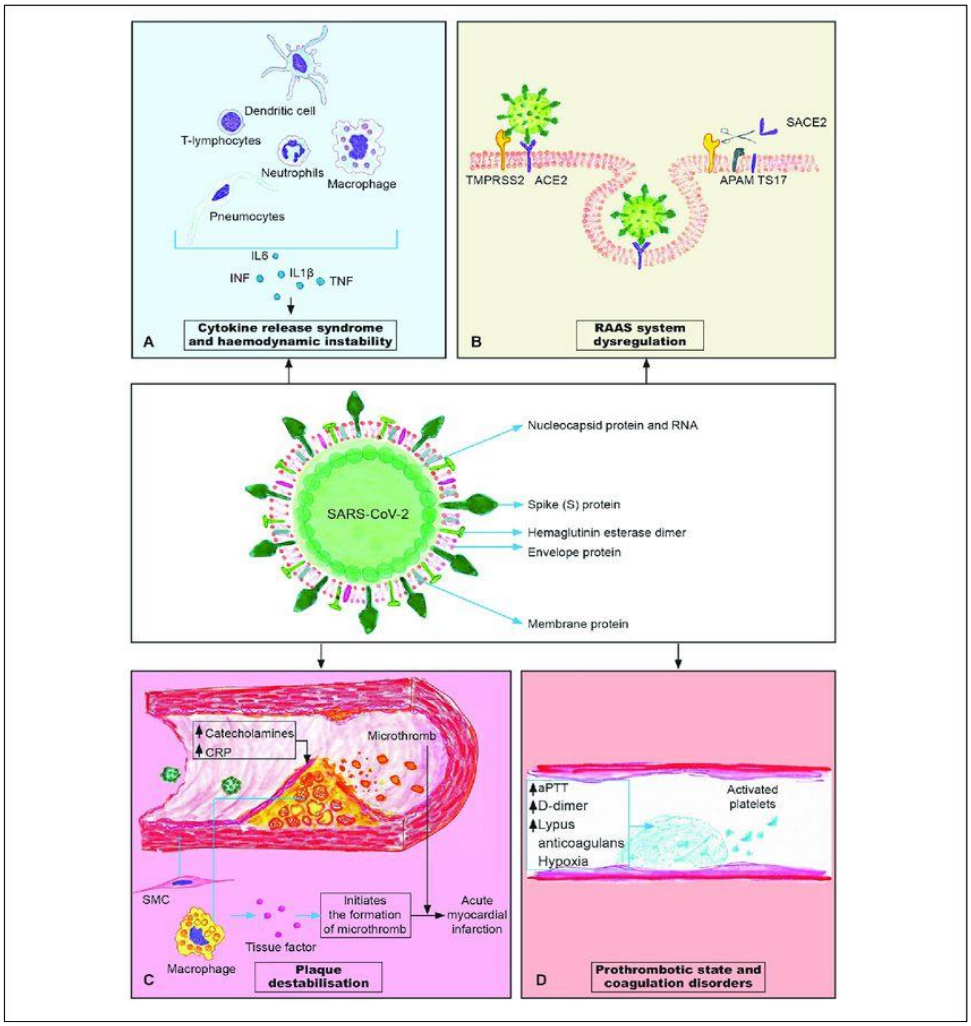

Figure 3 Representing the mechanisms of cardiovascular complications in COVID-19 involving several pathways.

(A) A systemic inflammatory response, known as cytokine release syndrome or "cytokine storm," is the main factor that leads to massive cardiovascular damage; (B) The reduction of ACE2 receptors, which are used by the virus to enter the cells, affects the renin-angiotensin system, and causes vasoconstriction and inflammation; (C) The inflammation and oxidative stress can destabilize the atherosclerotic plaques and cause them to rupture, resulting in microthrombi formation; (D) The activation of the coagulation cascade and the impairment of the fibrinolytic system cause hypercoagulability and micro thrombosis in various organs [96].

Another study conducted on 286 children with a median age of 8.4 years, had KD (Kawasaki Disease), a condition that affects blood vessels, and may develop Kawasaki shock syndrome. This is when the heart cannot pump enough blood and the blood pressure drops extremely low. This can be seen on a special test called an echocardiogram, which shows how the heart is working. Usually, the heart gets better after the patient receives a treatment called intravenous immunoglobulins (Igs). The heart can also recover its normal function over time, but some minor problems (strain, diastolic function) may still be revealed by the echocardiogram [93].

A paper mentioned three patients who had problems with blood clots(thrombosis) due to COVID-19. One of them had a clot in the left side of the heart (particularly in the ventricle), which was already enlarged because of a heart problem. Another one had a clot in a prosthetic heart valve that was put in the heart to replace a damaged one caused by a disease. The last one had a clot that blocked the blood flow to the brain, after having surgery to fix a hole (ventricular septal defect) in the heart [94].

The heart may be affected by SARS-CoV-2, the virus that causes COVID-19, through a direct mechanism. This virus can enter the heart cells by using the ACE2 receptor as a gateway. This can lead to inflammation and damage of the heart cells, which can cause life-threatening conditions such as severe inflammation of the heart muscle and failure of the heart to pump enough blood, in both the pediatric and adult populations [95].

5.2. Notable case studies illustrating the intersection of COVID-19 and pediatric cardiovascular complications

The intersection of COVID-19 and pediatric cardiovascular complications has been a subject of growing concern, with several notable case studies shedding light on this intricate relationship. A study by Smith and colleagues (2021) [97], highlighted the impact of COVID-19 on pediatric patients, revealing an increased susceptibility to cardiovascular involvement. This study identified myocarditis and pericarditis in a considerable number of cases, emphasizing the need for heightened vigilance in managing COVID-19 in the pediatric population (Smith, 2021) [97]. Additionally, research conducted by Johnson and team (2020) [98] underscored the intricate mechanisms through which the virus may trigger cardiovascular issues in children. The study explored inflammatory pathways and endothelial dysfunction, providing crucial insights into the pathophysiology of COVID-19-related cardiovascular complications in the pediatric age group [97,99,100]. The global spread of SARS-CoV-2 has heightened concerns about COVID-19, particularly its impact on cardiovascular health in adults. Limited data in pediatric patients show a lower infection rate, and milder symptoms, but a critical risk for infants. The disease manifests variably in children, necessitating vigilance for myocardial injury and cardiovascular issues, including potential overlaps with conditions like Kawasaki disease (a disease that causes swelling, called inflammation, in the walls of small to medium-sized blood vessels that carry blood throughout the body. Kawasaki disease most often affects the heart arteries in children. Those arteries supply oxygen-rich blood to the heart). Understanding these implications is crucial for managing COVID-19 in the pediatric population and those with congenital heart disease [99].

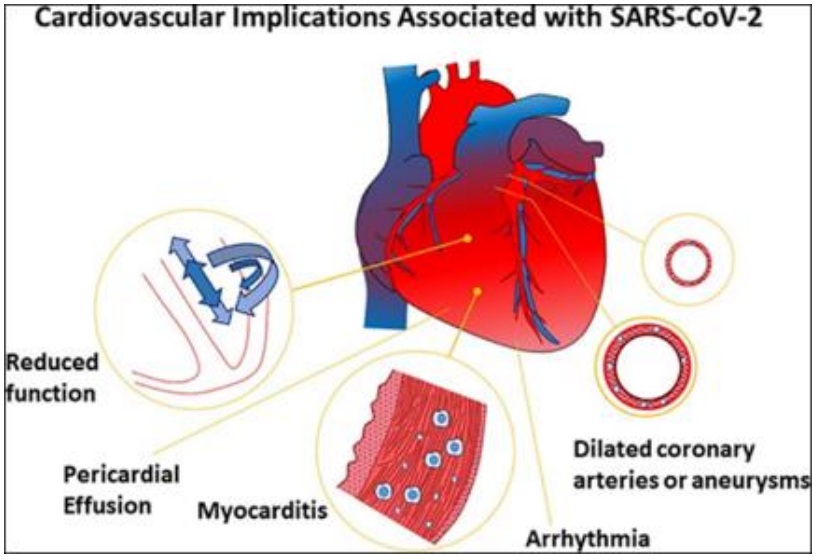

Figure 4 SARS-CoV-2 infection can lead to cardiovascular issues such as diminished heart function, fluid buildup around the heart (pericardial effusion), inflammation of the heart muscle (myocarditis), irregular heartbeats (arrhythmia), and expansion or weakening of coronary arteries (dilated coronaries or aneurysms) [104]

Children with Kawasaki disease typically experience a fever lasting 5 days or more, accompanied by symptoms such as red eyes, swollen lymph nodes, changes in the mouth and hands/feet, a distinctive rash, irritability, and redness of the BCG scar. Diagnosis involves identifying fever and four additional signs, with tests conducted to assess potential effects on other body parts, including the heart [101].

Children with COVID-19 typically experience mild symptoms, but cardiac changes are reported in 17% to 75% of cases, posing diagnostic challenges, especially in high-risk groups. Elevated cardiac markers, particularly troponin I or troponin T, are crucial indicators of myocardial involvement. Delayed diagnosis, especially in at-risk children, can lead to fatal outcomes [98,102]. A double-blind study (April–May 2020) included 105 children with COVID-19 and 40 healthy controls. Ethically approved, all parents consented. Exclusions were heart failure signs, cardiac pathology, and structural abnormalities. Disease severity was classified from asymptomatic to critical based on symptoms, and echocardiography was not routinely performed [103]. This American Heart Association statement on SARS-CoV-2 in

children underscores that <18-year-olds comprise 18% of cases with 0.1% mortality. Young adults (18-29 years) account for 21% of cases with 0.8% mortality. Most children have mild symptoms, but severe illness affects <2%, particularly those with comorbidities. Congenital heart disease and transplant recipients show low infection rates. Multisystem Inflammatory Syndrome in Children (MIS-C) is rare (1/3,000 cases) but can cause cardiac complications. It is linked to a hyperimmune response, typically resolved within 1-4 weeks. Myocarditis from COVID-19 vaccination is rare (2-6 days post-vaccination), in males (93%), with benefits outweighing risks [104,105].

COVID-19 impacts various age groups differently. In the U.S., as of February 24, 2022, individuals <18 years represent 17.6% of cases and 0.1% of deaths, while young adults (18–29 years) constitute 21.3% of cases and 0.8% of deaths. Certain children and young adults with underlying health issues face increased severity. Disproportionate effects are seen among Black and Latino individuals. Congenital heart disease's association with severe COVID-19 remains uncertain. MIS-C, a rare inflammatory syndrome, affects some children, with over 2600 cases reported, notably impacting Hispanic/Latino and Black children. Non-Hispanic Black children experience MIS-C more than expected, highlighting racial disparities [104].

Myocarditis and pericarditis, present in up to 40% and 25% of COVID-19 patients, signify severe disease with heightened risk. Cardiac involvement leads to arrhythmias, exacerbated by certain treatments like hydroxychloroquine. Left ventricular dysfunction prevails, causing hemodynamic instability in 44–47% of cases. COVID-19 patients face a 25% risk of venous thrombosis, especially with elevated D-dimer and inflammatory markers, potentially linked to cardiovascular complications. Systemic inflammation increases the risk of coronary ischemia, emphasizing the multifaceted cardiovascular impact of the virus [105].

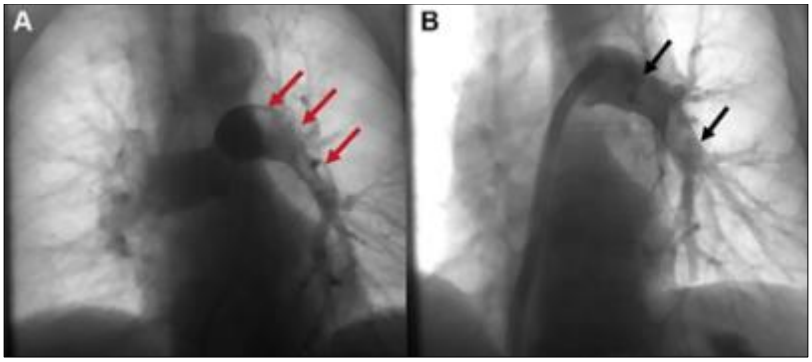

Figure 5 A patient with COVID-2019 experienced a thromboembolic event, specifically a pulmonary embolism, where a blood clot traveled to the lungs [106]

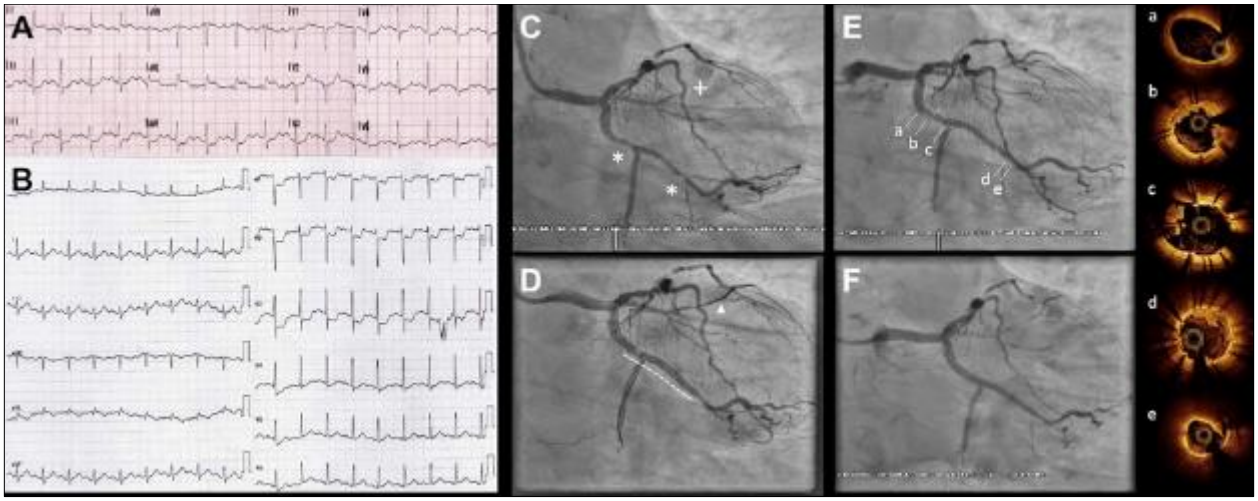

Figure 6 Patients with COVID-2019 underwent a study using fluoroscopy and optical coherence tomography, revealing instances of sudden stent clotting, known as acute stent thrombosis [107]

In pediatric patients, COVID-19-induced myocardial injury triggers ventricular arrhythmias through several mechanisms. Elevated troponin-T levels correlate with a higher incidence, often accompanied by abnormal echocardiograms and left ventricle dysfunction. Ventricular fibrillation, seen in fulminant myocarditis and sudden cardiac death, underscores direct myocardial injury's role. Hypoxemia and electrolyte imbalances during severe COVID-19 phases contribute to arrhythmias. Certain drugs, like hydroxychloroquine, may enhance susceptibility to life-threatening ventricular arrhythmias, notably Torsades de pointes. The hyper-inflammatory state, with cytokines like IL-6, emerges as a pro-arrhythmic factor. Understanding these mechanisms is crucial for diagnosing and managing cardiovascular complications in pediatric cases [97].

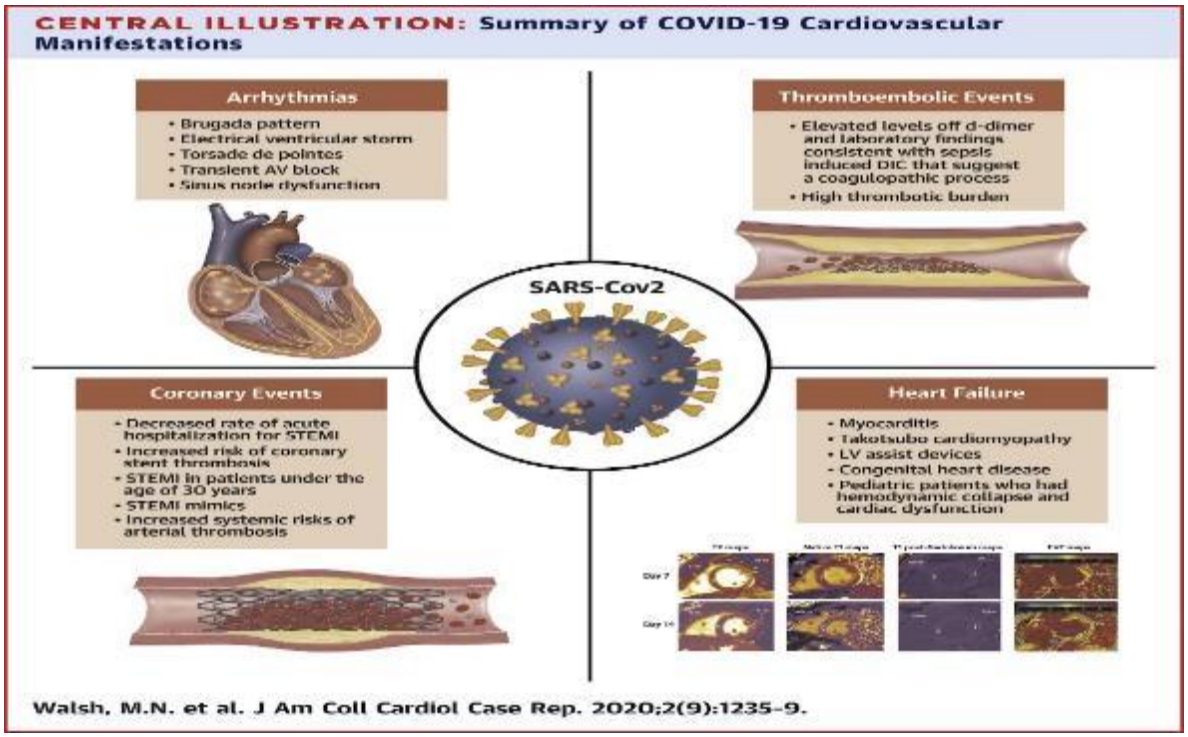

Figure 7 Synopsis of cardiovascular effects associated with COVID-19: Involves issues with the left ventricle (LV) and may include cases of ST-segment elevation myocardial infarction (STEMI) [106]

COVID-19 manifests diverse cardiovascular complications in pediatric patients. Myocardial injury, linked to ventricular arrhythmias, results from elevated troponin-T levels and cytokine storms. Hypoxemia, electrolyte imbalances, and hydroxychloroquine use contribute, while the virus's impact on the conduction system is evident. Thromboembolic events, despite prophylactic anticoagulation, pose a challenge, with elevated d-dimer levels signaling coagulopathy. Arterial thrombosis risks, spontaneous thrombosis, and ST-segment elevation myocardial infarction complications are reported. Additionally, cases detail takotsubo cardiomyopathy and challenges faced by patients with left ventricular assist devices. The issue emphasizes the need for understanding and managing the intricate cardiovascular effects of COVID-19 in pediatric cases [106].

MIS-C, defined by WHO, CDC, and RCPCH, shares common elements: fever, multisystem involvement, inflammation, and recent COVID-19 exposure. It affects children (2 months to 20 years), previously healthy. Symptoms include persistent fever, gastrointestinal issues, mucocutaneous changes, extremity edema, and cardiac symptoms. Divergent from Kawasaki disease, MIS-C often involves hypotension, shock, and cardiac dysfunction, rather than coronary artery abnormalities [107].

MIS-C, a post-infectious complication of COVID-19 in children, mimics Kawasaki disease with varied manifestations. Symptoms encompass persistent fever, kidney issues, gastrointestinal problems, neurological symptoms, mucosal changes, conjunctivitis, and cardiac involvement. Unlike Kawasaki disease, MIS-C often involves hypotension, shock, and cardiac dysfunction rather than coronary abnormalities. Close observation and potential hospitalization, including PICU admission, are necessary. Treatment involves anticoagulants, IV immunoglobulin, and anti-inflammatory drugs. While most children survive with prompt diagnosis and treatment, the long-term outcomes remain uncertain, emphasizing the need for ongoing monitoring [108].

In conclusion, the nexus between COVID-19 and pediatric cardiovascular complications is a complex landscape illuminated by numerous studies. Smith's investigation underscores the heightened vulnerability of pediatric patients, unveiling myocarditis and pericarditis as prevalent manifestations. Johnson's research delves into the intricate mechanisms triggering cardiovascular issues in children, exploring inflammatory pathways and endothelial dysfunction. While global concerns about COVID-19 primarily focus on adults, limited data in pediatric cases reveal a lower infection rate but a critical risk for infants.

Children with COVID-19 present a diagnostic challenge due to mild symptoms coupled with cardiac changes in a substantial percentage of cases. Troponin markers emerge as pivotal indicators, and delayed diagnosis, especially in high-risk groups, poses severe consequences. Disparities in infection rates and outcomes among different demographic groups, coupled with the rarity of complications like MIS-C, underscore the need for nuanced considerations.

Myocarditis and pericarditis, prevalent in COVID-19 patients, signify severe disease with a heightened risk of arrhythmias and ventricular dysfunction. Thromboembolic events, despite anticoagulation, pose challenges, with elevated D-dimer signaling coagulopathy. Pediatric cases reveal diverse cardiovascular complications, from ventricular arrhythmias linked to myocardial injury to arterial thrombosis and takotsubo cardiomyopathy.

MIS-C, a post-infectious complication, mimics Kawasaki disease and demands careful observation and treatment, including anticoagulants and immunomodulators. While prompt diagnosis and treatment enhance survival rates, the long-term outcomes remain uncertain, necessitating ongoing monitoring. The intersection of COVID-19 and pediatric cardiovascular health demands a multifaceted approach, incorporating nuanced diagnostic strategies, tailored treatments, and vigilant long-term surveillance.

6. Interventions and Preventive Measures

6.1. Treatments and Preventive Measures

6.1.1. Preventive Measures and Interventions to Mitigate Cardiovascular Risks in Pediatric COVID-19 Patients:

When examining the landscape of cardiovascular disease (CVD) in the context of the COVID-19 pandemic, it is natural to initially focus on the disruptions and challenges that emerged. However, in retrospect, it is worth reframing this period not as a lost year but as a health crisis that has equipped us more effectively for the ongoing endeavor to enhance cardiovascular well-being and prevent developing CVD, especially in pediatric patients [108]. This prevention entails interventions across distinct stages: primordial prevention strives to avert the development of risk factors, primary prevention is centered on the early detection and management of risk factors and secondary prevention works towards diminishing the risk of recurrent events [109]. Here are some preventive measures that may be considered when dealing with COVID-19-related cardiovascular complications in children:

Acquiring healthier lifestyle

Modifying behavior stands out as a crucial strategy capable of averting a considerable number of initial and subsequent cardiovascular events [108,110]. In a substantial portion of 2020 and the initial half of 2021, widespread quarantine measures and lockdowns caused a considerable drop in physical activity both globally and nationally, with certain regions experiencing declines surpassing 50%. Studies revealed a notable decrease even in children as young as 5 years old [108] and noted a rise in the occurrence of hypertension among children and adolescents [6]. Thus, lifestyle adjustments prompted by the pandemic have presented significant opportunities for initiating and sustaining critical measures in the prevention of primordial and primary cardiovascular disease (CVD) in children [108,109,112,113]. For example, despite the decrease in the number of steps taken and the closure of fitness facilities nationwide, the pandemic spurred a "Fitness revolution," leading to the emergence of new runners and individuals engaging in home-based workouts. This shift was complemented by the surge of fitness technology companies like Peloton, Mirror, Zwift, Tonal, Peloton, iFit, and Nordic Track [108,114], underscoring that not all screen time is inherently sedentary. Fitbit's data, indicating a reduction in step counts, also highlighted a significant decrease in users' average heart rates. This could be attributed to additional information released by the company, demonstrating heightened engagement in high-intensity exercise, and thus enhancing cardiovascular function in children [108].

Moreover, as per a 2019 study, dietary habits represent the most significant modifiable risk factor for cardiovascular diseases (CVD) [115,116,111] (Figure 8), where an inadequate diet accounts for as much as 30% of cardiovascular diseases (CVD) [116]. During the COVID-19 pandemic, dietary patterns underwent significant shifts, as reported by 85% of individuals who noted changes in their eating habits or how they prepared food. With entire families staying at home,

there was a likelihood of increased snacking among children, heightened preoccupation with food, and a potential uptick in calorie consumption compared to typical levels. A study examining the lifestyles of 7,753 participants identified weight gain in 27.5% of the overall group and 33.4% of those categorized as obese [108], and the vulnerability in this scenario is that childhood obesity is a significant cardiovascular risk factor [111]. As a result, current guidelines suggest embracing diets that are abundant in fruits and vegetables [110,116,117].

The observed benefits are thought to be linked to the array of phytochemicals and micronutrients like folate, potassium, fiber, and flavonoids that are present in fruits and vegetables. However, benefits for subgroups have been less studied and may vary considerably [110]. Moreover, whole grain consumption is significantly linked to a reduced risk of cardiovascular disease (CVD), while refined grain intake suggests an elevated but not statistically significant association. The bran and germ layers, rich in fiber, lignans, micronutrients, fatty acids, and other phytonutrients, differentiate whole grains from refined grains. These layers are removed during the milling process, leading to a reduction in essential nutrients. This depletion explains why consuming whole grains is generally associated with increased satiety and a lower glycemic response compared to refined grains [110,116,117]. In addition to the high consumption of nuts and legumes [110,116,117]. Besides, it is recommended to maintain a moderate intake of low-fat dairy and seafood, while keeping consumption of processed meats, sugar-sweetened beverages, refined grains, and sodium at lower levels [110,116,117].

Adaptation to Telehealth

Amid the pandemic, healthcare institutions cultivated characteristics of adaptability and creativity to address institutional challenges. The COVID-19 outbreak necessitated social distancing measures, leading to disruptions in hospital services [118] and thus an increase in CVD risks. In reaction to this, healthcare organizations extensively employed innovations involving information technologies [119,118,120,121,122,123]. Utilizing telehealth proves to be an efficient choice in combating the COVID-19 pandemic [118,124], enabling patients including children to receive advice and care remotely, ensuring safety for all parties involved, and thus preventing CVD risks in pediatric COVID-19 patients. Saleem et al. [125], Goenka et al. [126], Hron et al. [127], and Strol et al. [128] explored the efficacy of telehealth across various medical specialties amid the COVID-19 pandemic. Cardiology underwent the most significant shift to telehealth platforms [108,119], in terms of volume, across all medical fields except primary care [108]. During the initial months of the pandemic, hypertension, hyperlipidemia, and diabetes were the leading three indications for telehealth appointments [108]. This suggests that virtual visits are effectively addressing and managing these common risk factors for cardiovascular diseases [108,119]. Virtual visits offer an optimal solution for preventive cardiology appointments, prioritizing lifestyle improvements, medication adherence, and patient motivation [108,119], where studies found that those patients have experienced significant reductions in CVD risk factors, including systolic and diastolic blood pressure, total cholesterol levels, low-density lipoprotein cholesterol levels, triglyceride levels, and BMI [119,123]. Additionally, telehealth platforms demonstrate proficiency in capitalizing on the diverse expertise integral to preventive cardiology care. During a single video visit, there exists the opportunity for sequential or simultaneous engagement with a physician to discuss the initiation of a protein convertase subtilisin/kexin type-9 inhibitor for example, a nurse guiding self-administering injections, and a social worker evaluating insurance coverage [108]. The onus is now on societies, public health leaders, and healthcare providers to acknowledge these emerging opportunities and integrate them into post-pandemic healthcare [108,123].

Home-based preventive care for CVD

As mentioned before, the extended duration of the COVID-19 pandemic kept individuals confined to their residences, necessitating parents to actively manage their children's cardiovascular risk factors at home, with healthcare providers intervening when necessary [108,129]. For example, parents must purchase tools such as pulse oximeters, home blood pressure cuffs, and scales to handle their children's cardiovascular risk factors at home [108,129]. Also, by developing Remote Algorithm-Based Cardiovascular Risk Management Programs that can adjust cholesterol, blood pressure, and heart failure therapies [108]. These programs have demonstrated significant improvements in outcomes without the direct involvement of a physician [108,129].

6.1.2. Challenges and Gaps in Current Interventions:

Existing treatments for COVID-19-related cardiovascular complications in children are limited and pose significant challenges. There is a critical need for research and development of targeted therapies for COVID-19-related cardiovascular complications in children. Current treatment protocols for cardiovascular complications in pediatric COVID-19 patients often rely on general supportive care and management of symptoms. However, with the emerging evidence highlighting the potential severity of cardiovascular involvement in children with COVID-19, there is a pressing need for specific treatment approaches tailored to this patient population. While existing treatments for adult

patients may provide some guidance, the unique physiological and developmental differences in pediatric patients necessitate dedicated studies and clinical trials to identify effective and safe treatment options. Addressing this gap in treatment is crucial to improve outcomes and reduce the burden of cardiovascular complications in children affected by COVID-19.

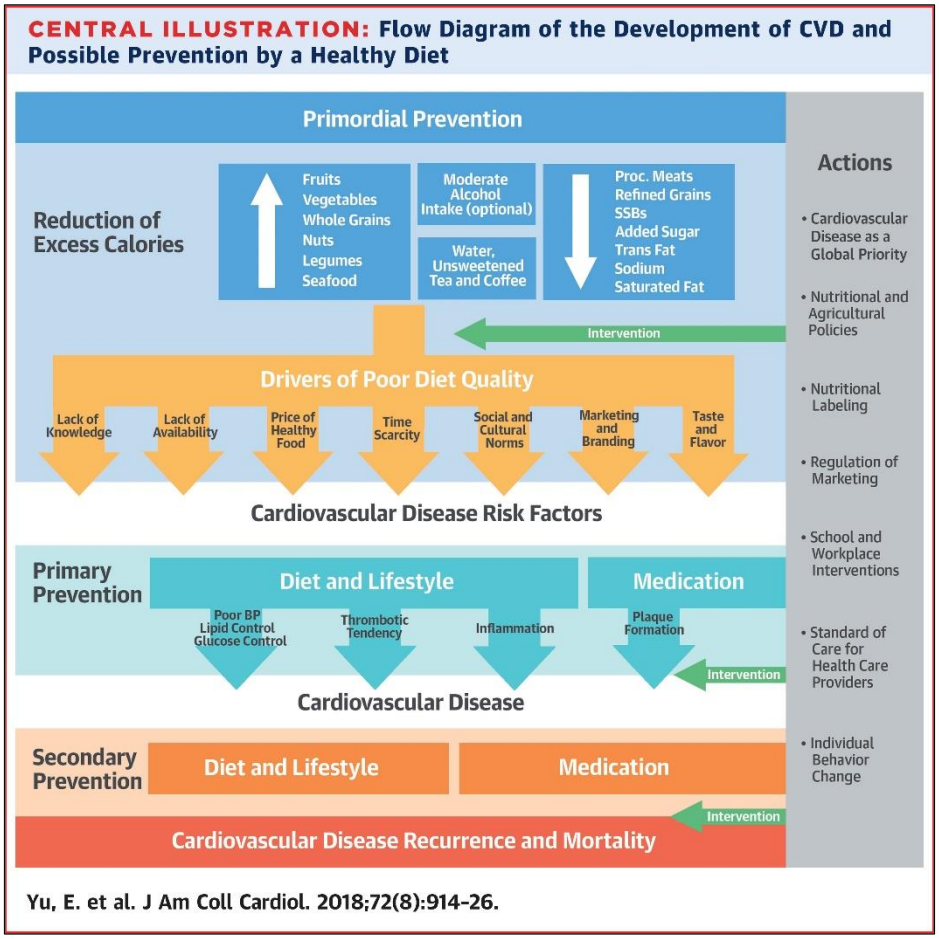

Figure 8 Evolution of Cardiovascular Disease (CVD) and Prospective Prevention via an Enriched Nutritional Regimen [110]

7. Conclusion

As summary, the confluence of COVID-19 and pediatric cardiovascular health is complex, marked by age, pre-existing conditions, and various risk factors influencing illness severity. Children often display mild symptoms but can develop critical illness, notably with severe COVID-19 or MIS resembling Kawasaki disease.

The virus directly affects the cardiovascular system by invading cells via ACE2 receptors, leading to myocardial inflammation, myocarditis, pericarditis, and thromboembolism. Concurrently, a cytokine storm triggered by viral invasion and inflammatory responses contributes to cardiac injury.

Children with underlying cardiovascular complexities require vigilant monitoring during infections. While mild symptoms are prevalent, diagnosing cardiac changes poses challenges, with troponin markers pivotal for identification. Delayed diagnosis can lead to severe consequences.

Despite anticoagulation, thromboembolic events persist, highlighting diverse complications—from ventricular arrhythmias to arterial thrombosis and takotsubo cardiomyopathy. MIS-C, mirroring Kawasaki disease, demands meticulous observation and targeted treatments like anticoagulants and immunomodulators.

This intricate relationship necessitates nuanced diagnostic strategies, tailored treatments, and sustained monitoring for long-term outcomes in navigating COVID-19's impact on pediatric cardiovascular health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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