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Cardiac Aspect of Coronavirus Disease 2019 (COVID-19) in Children

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Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic with more than a million confirmed cases of COVID-19 and more than 130,000 deaths reported worldwide. The major morbidity and mortality from COVID-19 are large because of acute viral pneumonitis that evolves to acute respiratory distress syndrome. Cardiac injury is one of the common complications of COVID-19. Furthermore, preexisting cardiovascular disease is one of the important risk factors for mortality among the patients. Evidence of cardiac involvement is common among patients hospitalized with COVID-19, but the causes of myocardial injury have not been completely explained. COVID-19 appears to be milder in children than in adults and fewer children seem to have developed severe respiratory distress. The aim of this article is a brief review of cardiovascular involvement in COVID-19 with a focus on cardiac disease in children.

Keywords: COVID-19; Corona virus disease 2019; Cardiac complication; Cardiovascular disease; Arrhythmia; Mortality; Child.

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Introduction

At the end of 2019, an outbreak of severe pneumonia caused by a novel coronavirus occurred in china and has spread quickly throughout the world with more than 130,000 deaths reported worldwide. This new virus belongs to the severe acute respiratory syndrome-coronavirus (SARS-CoV) and the Middle East respiratory syndrome-coronavirus (MERS-CoV) family. The World Health Organization designated the disease term COVID-19. Four types of human CoV types are endemic in humans and usually cause mild upper respiratory infections and account for 15-30% of common colds. The most severe form of systemic viral infection appears as acute respiratory distress syndrome (1).

People of all ages are susceptible to COVID-19. The elderly and those with underlying chronic diseases are more likely to become severe cases (2). Early data suggest that the viral infection in children are less severe than those in adults (3). The latest systematic review showed that children have accounted for 1-5% of diagnosed COVID-19 cases and deaths have been extremely rare (4).

The most common clinical features reported at the onset of illness include fever, fatigue, dry cough, anorexia, myalgia, and dyspnea. Pneumonia is the most frequent and serious manifestation of COVD-19 characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging (1, 2).

With the growing number of infected patients, major cardiac complications have been reported in patients with cardiovascular diseases and also in those without any underlying conditions (4,5).

Previous studies have revealed that myocardial infarction and myocarditis are associated with SARS-CoV and MERS-CoV outbreaks. Also, a significant association between underlying cardiovascular diseases with myocardial injury leading to worse outcomes were observed during those outbreaks (6,7). Therefore, early diagnosis of cardiac complications along with understanding the true mechanisms of infection-related cardiac injury appears to be essential for improving outcomes. It is crucial to consider that during of recent outbreak, diagnosis of a cardiac illness can be particularly challenging because of similar presentations of both of the diseases with overlapping radiologic findings. The aim of this article is a brief review of cardiovascular involvement in COVID-19 with a focus on cardiac disease in children. We searched Medline (used by PubMed) and Google scholar databases for relevant terms related to COVID-19 up to Apr 12, 2020, using the keywords "COVID-19", and "cardiovascular system" and/or "children". There are a few articles that describe clinical features and common complications in children infected with COVID-19.

Cardiac injury

Myocardial injury is likely associated with multiple mechanisms including infection-related myocarditis, systemic inflammatory response, ischemic microvascular damage or hypoxic injury and other factors (8-12). Acute myocardial injury was defined as elevated troponins (TnT, TnI) greater than the 99th percentile upper limit. Previous studies showed that elevated cardiac troponin level is a sensitive biomarker of myocardial injury, however, it does not distinguish among the causes of injury. Cardiac biomarker studies suggest a high prevalence of cardiac injury in hospitalized patients, most of them had critical respiratory distress (8,9).

The study of Chen et al. revealed elevated cardiac enzymes in 13% of patients who were admitted to the hospital (13-15). In another series, Huang et al. showed that 31% of patients who required ICU care had elevated troponins compared to 4% of those who did not (16). Considering recent data, mortality is significantly increased in individuals with high troponin levels compared with those with normal values. The patients with high troponin levels were older and had higher comorbidities including hypertension, coronary heart disease, cardiomyopathy, and chronic kidney disease (8,11,16). These data suggest the fundamental role of cardiac protective management to reduce the case fatality rate in critically ill patients.

Furthermore, cardiac involvement has also a significant effect on outcomes. In the study of Shi et al. on 416 hospitalized patients, the cardiac injury was defined in 20% of the patients and of whom 57 cases died. In these patients, 10.6%had coronary heart disease, 4.1% had heart failure, and 5.3% had cerebrovascular disease (10). More prevalence of cardiac complications (33%) was noted in the US cohort of 22 patients with a mean age of 70 years (13). The difference may relate to underlying comorbidities (86%) or to the older age of that population. Similarly, Guo et al. reported factors associated with outcomes in 187 hospitalized patients from china (43 died; 144 discharged). Of whom, 28% showed evidence of acute myocardial injury and 35% had underlying cardiovascular diseases including hypertension, coronary heart disease, or cardiomyopathy (14).

Early reports indicate that there are various patterns of myocardial injury with COVID-19. Both of the high troponin values associated with an increased level of inflammatory biomarkers (D-dimer, ferritin, interleukin-6) are suggested as a systemic inflammatory response or a cytokine storm. A cytokine storm, defined as an imbalanced response among subtypes of T helper cells, may lead to cardiac myocyte apoptosis (12,17-19). In contrast, other studies on patients presenting with predominantly cardiac symptoms (chest pain and/or ST elevation on ECG) have suggested a different pattern of cardiac involvement, potentially viral myocarditis or stress cardiomyopathy (12,20,21). Another proposed mechanism is hypoxia-induced myocyte apoptosis that is probably more obvious in whom with severe pneumonia. Otherwise, both acute respiratory distress syndrome and superimposed pulmonary infection along with increased sympathetic stimulation may inappropriately raise myocardial oxygen demand. (19-22). The additional mechanism of acute myocardial injury caused by COVID-19 may be related to the ACE2 receptor. ACE2 receptor is a functional receptor for coronaviruses and also is widely expressed not only in the lungs but also in the cardiovascular system (23).

Additionally, a combination of a significant systemic inflammatory response plus localized

vascular inflammation at the arterial plaque level has proposed as a leading cause of myocardial infarction (17,18).

Recent reports have obtained a considerably greater prevalence of the preexisting cardiovascular disease in patients with evidence of myocardial injury compared with those without elevated biomarkers (10). Nevertheless, it is not yet possible to determine whether the myocardial injury is an independent risk factor in COVID-19 or the risk associated with it is related to the burden of preexisting cardiovascular disease. Further investigation is required to determine the relationship between COVID-19 and myocardial injury and its true mechanisms.

Heart failure

Limited data are available on the incidence of heart failure in patients with COVID-19. In a retrospective study of 799 patients hospitalized with COVID-19, heart failure was observed as a complication in 49% of patients who died and in 3 percent of patients who recovered (24). Elevated natriuretic peptides, as a biomarker for heart failure, have been identified in patients with evidence of cardiac injury (10). Heart failure in patients with COVID-19 may be exacerbated by acute viral illness in patients with pre-existing known or undiagnosed heart disease (eg, coronary artery disease). Similarly, a high prevalence of cardiovascular risk factors and cardiac diseases are observed in hospitalized patients with COVID-19 (19).

Cardiac Involvement in Children

Based on published studies, children accounted for less than 5% of diagnosed COVID-19 patients (25). The largest reported group was a Chinese paper by the *Chinese Novel Coronavirus Pneumonia Emergency Response Epidemiology Team* with 72,314 cases and this found that about 2% of the laboratory-confirmed cases of COVID-19 were children aged 0-19 years (5). COVID-19 appears to be milder in children than in adults and fewer children seem to have developed severe respiratory distress (12,26,27).

The reasons for a less severe clinical course of COVID-19 in children are not fully recognized. Some considerations are a lesser immune response to the virus in children that may lead to mild inflammatory response, less severe pulmonary damages resulting in less severe hypoxemia (25,28). Another explanation is possible resistance of the lower respiratory tract to the viral infection that leads to lower viral load in children compared to adults. Various expression of ACE2 receptor in the respiratory tract of children for COVID-19 appears to have a remarkable impact on disease severity (28-30).

Previous reports revealed that younger children and those with certain serious underlying conditions are at greater risk for severe illness (30-31). The most commonly reported underlying conditions were a chronic pulmonary disease, cardiovascular disease, and immunosuppression (31,32). Because of mild clinical course of children with COVID-19 and small groups of hospitalized children, the presence of a certain type of cardiac complication and also preexisting cardiovascular conditions seem to have more investigated in the future. Furthermore, probable differences in clinical course of children who experiencing any congenital heart disease are not yet fully described.

Consequently, the cardiovascular character of COVID-19 in pediatric patients should be further clarified after collecting more pediatric case data.

Arrhythmias

The prevalence of arrhythmias and conduction system disease in patients with COVID-19 varies between reports depending on several factors including the specific type of arrhythmia, age of the patients, clinical status and preexisting comorbidities (8,32,33).

The majority of patients presenting with symptoms consistent with COVID-19 will not have symptoms or signs of conduction system abnormalities. In a case series of 138 patients who were hospitalized with pneumonia, arrhythmias were observed in 17 percent of the general cohort and 44 percent of patients admitted to ICU (8). In another study of 138 hospitalized subjects, 7% of patients have palpitation as a presenting symptom, but certain types of arrhythmias were not specified (32).

The most commonly reported arrhythmia in patients was sinus tachycardia, which is expected in the setting of a systemic illness (eg, fever, pain, etc). Otherwise, the most likely pathologic arrhythmias include atrial fibrillation, atrial flutter, and ventricular tachycardia (VT) (32).

Metabolic disturbances and electrolyte abnormalities along with hypoxemia have identified

to contribute to the development of arrhythmias in patients with a critical illness, although, the impact of cardiac myocyte injury for developing any rhythm disturbances in mildly symptomatic or severely ill patients is not completely recognized (32-34). A higher incidence of VT was reported in patients with elevated troponin-T levels (35). However, the evidence provided that in ICU patients, despite the high frequency of arrhythmias, only a half showed acute cardiac injury, suggests that factors other than myocardial damage are also involved in enhancing the arrhythmic risk in COVID-19 (35,36).

In recent reports, the potential role of pharmacological treatments in enhancing the susceptibility to QT-related life-threatening arrhythmias is increasingly evaluated. The drugs such as chloroquine, hydroxychloroquine, macrolides as well as fluoroquinolones, are well-recognized QT-prolonging medications frequently administered to patients (36-39). The influence of them becoming more significant when it considered that the patients receiving these drugs are likely those with more severe illness with the presence of other concomitant risk factors for QTc prolongation such as electrolyte imbalances.

Furthermore, a potentially pro-arrhythmic factor is a high burden of systemic inflammatory state in COVID-19. Evidence obtained from recent studies revealed that inflammation is an important risk factor for long QT-syndrome and polymorphic VT, primarily via direct electrophysiological effects of cytokines on the myocardium (40,41). Besides the direct cardiac effects of severe viral infection, systemic inflammation might additionally predispose to malignant arrhythmias as a result of indirect mechanisms (41).

Previous data on hydroxychloroquine suggest it has a low risk for developing polymorphic VT (37,38). However, there can be greater QT-prolonging effects in those with electrolyte abnormalities, those taking QT-prolonging antibiotics, those with chronic renal insufficiency, and those with congenital long QT syndrome. Therefore, the patient's baseline QT interval value should be obtained and also any new symptoms including palpitation promptly recorded (39). Patients with baseline QTc interval ≥500 msec are at increased risk for significant QT prolongation and polymorphic VT. Acquired QT prolongation is reversible upon discontinuation of an offending medication or correction of electrolyte derangements (42-44).

Cardiac Comorbidities

Based on various published studies, advanced age (>60years), male sex, and the presence of comorbidities are recognized to be the major risk factors for COVID-19 fatality (2,45,46). Accordingly, chronic medical illnesses are common in patients who are admitted to hospital and also Patients treated in the ICU compared with patients not treated in the ICU (n = 102) were more likely to have underlying comorbidities (2).

In a large study of 1099 patients with a different spectrum of clinical illness, the most common comorbidities include hypertension (14.9%), diabetes (7.4%), and coronary heart disease (2.5%). But, the basic cardiac disease has not appeared as a determining factor of fatality and the overall mortality rate was 1.4% (2). Concerning data obtained from a meta-analysis including 76993 patients, the prevalence of hypertension and cardiovascular disease was estimated at 16.3% and 12.1%respectively (46).

Otherwise, in one retrospective study of 150 critically ill patients, cardiovascular disease was more prevalent in patients who died (13 of 68) than patients who survived (0 of 82) (34). Similar prevalence of basic cardiovascular disease (14.5%) was reported by Wang et al. (8).

Based on obtained data, comorbidities were more prevalent in study subjects with advanced age or who are admitted to hospital because of a more severe progression of disease. Whether direct cardiovascular effect of viral infection or exacerbation of the underlying cardiac disease by the illness is led to poor outcomes needs to be investigated in the future.

Conclusion

Cardiac involvement is the major complication of COVID-19. Multiple direct and indirect cardiovascular complications including acute myocardial injury, myocarditis, arrhythmias have determined in COVID-19, however, the specific cause of myocardial damage is not yet recognized. Patients with both of the underlying cardiovascular and COVID-19 have an adverse prognosis. Our understanding of COVId-19 in children is limited because of small population of children with moderate to severe illness.

Therefore, particular attention should be given to understand the interplay between cardiovascular diseases and COVID-19, early diagnosis of cardiac complications and also cardiac protection during treatment.

Conflict of Interest

The authors declare no conflicts of interest.

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