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A Study on the Prevalence of Cardiac Complications in Children Hospitalized with COVID-19 at Motahari Hospital, Urmia, Between 2019 and 2021

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Abstract

Introduction: Nearly all pediatric age groups, including infants, are susceptible to contracting COVID-19. Considering the significance of exploring the secondary complications of COVID-19, especially in children, and the evidence suggesting the occurrence of MIS-C (Multisystem Inflammatory Syndrome in Children) and cardiovascular issues following COVID-19 infection in children, this study was carried out to assess the prevalence of cardiac complications in children hospitalized with COVID-19 at Motahari Hospital in Urmia between 2019 and 2021.

Materials and Methods: This was a cross-sectional and analytical study. The study included all children hospitalized at Shahid Motahari Hospital in Urmia from 2019 to 2021 with a confirmed diagnosis of COVID-19. The necessary data were obtained from patient records, and the results were analyzed using SPSS software version 27.

Findings: A total of 194 children hospitalized with a COVID-19 diagnosis were included in the study. Of these, 63.3% were in the 1 to 5-year age group, and 59.4% were boys. Approximately 18.8% had a history of known cardiovascular issues, and among them, 10.8% developed cardiac complications related to COVID-19. The most common cardiac complication was TR_PI (Tricuspid Regurgitation and Pulmonary Insufficiency), with an estimated prevalence of 60%.

Conclusion: Cardiovascular involvement in children with COVID-19 was not highly prevalent, and the changes observed during the acute inflammatory phase were mostly temporary.

Key words: *Children, COVID-19, Inflammatory Process, Multisystem Involvement, Cardiac Complications*.

Introduction

In December 2019, the widespread pneumonia outbreak in China attracted global attention (1). Research into the cellular invasion mechanism of COVID-19 revealed that, like SARS, this virus utilizes the angiotensin-converting enzyme 2

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(ACE2) receptor to enter cells (2). COVID-19 can affect nearly all pediatric age groups, including infants.

Among children, the highest proportion of cases has been observed in the 9 to 19-year age group. Furthermore, one of the largest studies conducted in China found that children under 19 years accounted for 2% of all confirmed COVID-19 cases (3). Studies indicate that most pediatric cases are either mild or asymptomatic (4). Research into the cellular invasion mechanism of COVID-19 reveals that, like SARS, this virus uses the ACE2 receptor to enter cells (2). The spike glycoprotein (S-protein) on the surface of the virus binds to ACE2. The receptor and enzyme, located on the surface of type 2 alveolar cells, trigger a structural change in the spike glycoprotein, leading to proteolytic cleavage by host cell proteases, ultimately resulting in virion internalization (5).

As a result of this viral pathogenesis mechanism, organs with high levels of ACE2 expression on their surfaces—such as the lungs, heart, gastrointestinal tract, and pancreas—are primarily affected. Consequently, various studies have identified fever, cough, shortness of breath, fatigue, and, in some cases, cardiomyopathy and gastrointestinal symptoms like vomiting, as the most common symptoms in COVID-19 patients, along with mental health issues such as anxiety disorders (6). Around 7–14 days after the onset of initial symptoms, more severe symptoms may develop due to a cytokine storm (7).

Nearly all pediatric age groups, including infants, are susceptible to contracting COVID-19. Among children, the highest proportion of cases (50 to 80%) has been reported in the 9 to 19-year age group. Moreover, in one of the largest studies conducted in China, children under 19 years of age made up 2% of all confirmed COVID-19 cases (8). While the epidemiological characteristics, laboratory parameters, clinical course, risk factors for prognosis, and the efficacy and safety of vaccination in adults have been well discussed (9,10), the clinical progression of COVID-19 in children, effective treatment regimens, and risk factors for poor prognosis are still being explored. Studies have indicated that most COVID-19 cases in children are mild or asymptomatic (11). However, several factors underscore the importance of this disease in children, including the potential for children to act as silent carriers of COVID-19, evidence of severe pulmonary manifestations, especially with new variants of the virus, the occurrence of significant subacute and chronic complications from COVID-19 despite asymptomatic infection, and the rising incidence of Multisystem Inflammatory Syndrome in Children (MIS-C) in COVID-19-positive children, highlighting the importance of this age group (12,13–14).

Children and adults have varying levels of immunity, which may account for the differences in the severity of clinical manifestations (15). The immature immune system of infants makes them more vulnerable to infectious diseases, particularly viral respiratory infections (16,17). Vertical transmission of respiratory viruses like COVID-19 to

newborns born to infected mothers has not been reported, and none of these infants have exhibited clinical signs of infection (18). COVID-19 can manifest in children in two distinct phases. In the first week, respiratory symptoms appear, generally less severe than in adults. However, 2 to 3 weeks later, symptoms of MIS-C (Multisystem Inflammatory Syndrome in Children) may emerge (19). Children with MIS-C typically present with persistent fever, lethargy, widespread polymorphic erythematous rash, non-purulent conjunctivitis, gastrointestinal symptoms, mucosal changes, and peripheral edema resembling Kawasaki disease (20,21).

In children with MIS-C, over 35% have reported left ventricular systolic dysfunction, 6% to 24% have coronary artery aneurysms, and 7% to 60% have experienced ventricular arrhythmias and electrocardiographic abnormalities, including ST elevation, prolonged QT interval, and premature atrial and ventricular contractions (22). Overall, studies have indicated that cardiac involvement is present in COVID-19 patients. This includes elevated cardiac biomarkers (such as cardiac troponin, creatine phosphokinase, and proteins), echocardiographic abnormalities (such as reduced left ventricular function, segmental or global wall motion abnormalities, and coronary artery dilation), and electrophysiological disturbances (including sinus tachycardia, atrial arrhythmias, non-sustained ventricular tachycardia, first-degree atrioventricular block, premature atrial and ventricular contractions, and incomplete right bundle branch block) (23).

The interaction of COVID-19 with the renin-angiotensin-aldosterone system (RAAS) can result in hypokalemia, which increases the risk of arrhythmias (24). Myocardial involvement in COVID-19 can be caused by acute viral myocarditis, hypoxemic injury (due to COVID-19 pneumonia), ischemic damage from coronary involvement, pulmonary hypertension and cor pulmonale, stress cardiomyopathy, and systemic inflammatory response syndrome (SIRS) (24). Studies have confirmed that cardiac involvement in COVID-19 patients includes elevated cardiac biomarkers, creatine phosphokinase, and proteins; echocardiographic abnormalities (such as reduced left ventricular function, segmental or global wall motion abnormalities, and coronary artery dilation); and electrophysiological disturbances (such as sinus tachycardia, atrial arrhythmias, non-sustained ventricular tachycardia, first-degree AV block, premature atrial and ventricular contractions, and incomplete right bundle branch block) (25).

Hypoxia may lead to calcium ion influx in cardiomyocytes, causing their apoptosis (26). Myocardial injury can result from a cytokine storm, triggered by an imbalanced response of T-helper 1 and T-helper 2 cells to the infection (24). One of the major complications of COVID-19 is endothelial hemostatic dysfunction, which can result in vascular thrombosis (25). The most common laboratory abnormalities in children include leukopenia, lymphopenia, thrombocytopenia,

elevated lactate dehydrogenase, and alanine aminotransferase levels (18). The initial chest radiographs of children with MIS-C often reveal non-specific findings, such as ground-glass opacities, reactive airway disease, pleural effusion, or normal appearances (18, 20, 26). Similar to adults, children with comorbidities—including chronic kidney or lung disease, malignancies, diabetes, obesity, anemia, immunodeficiencies, heart disease, and congenital anomalies—are more susceptible to severe forms of COVID-19 (19).

In a study conducted in Iran, the most commonly prescribed antibiotics for preventing secondary bacterial pneumonia due to COVID-19 were ceftriaxone, vancomycin, meropenem, and azithromycin, usually in combination. The most frequently used antivirals were Kaletra (lopinavir/ritonavir) and atazanavir (15). Increased CRP levels, older age, underlying conditions, and the severity of COVID-19 pneumonia are considered significant risk factors for cardiac involvement in COVID-19 patients (27).

In a 2020 study conducted in Tehran, 45 children hospitalized across three Iranian pediatric hospitals who met the criteria for MIS-C were evaluated. The mean age of the children was 7 years, with 53% being boys. Comorbidities such as acute lymphoblastic leukemia, chronic kidney disease, underlying seizure disorders, cerebral palsy, cardiovascular disease, and Budd-Chiari syndrome were present in 13% of the cases. Common symptoms included fever, abdominal pain, nausea, vomiting, mucocutaneous rashes, conjunctivitis, and leg edema. Most MIS-C patients presented with Kawasaki-like disease. Among these patients, 56% had cardiac involvement, with coronary artery dilation and myocarditis observed in 31% and 18% of the patients, respectively (28).

Reduced susceptibility in children is likely due to a lower presence of ACE2 receptors in their respiratory systems (18, 26). The most common laboratory abnormalities in children include leukopenia, lymphopenia, thrombocytopenia, elevated lactate dehydrogenase (LDH), and alanine aminotransferase (18). Most children with MIS-C, in addition to elevated C-reactive protein (CRP) and procalcitonin levels, also show elevated levels of B-type natriuretic peptide, ferritin, D-dimer, and cardiac troponin (21, 29).

Initial chest radiographs in children with MIS-C often reveal non-specific findings such as ground-glass opacities, reactive airway disease, pleural effusion, or normal results (18, 20, 30). Treatment for MIS-C patients related to COVID-19 involves immunomodulatory drugs and intravenous immunoglobulin (IVIG), with corticosteroids being used less frequently. In some reports, anti-inflammatory doses of aspirin have proven effective. Inotropic drugs are administered in cases of ventricular failure, and antiplatelet doses of aspirin are given to patients with Kawasaki-like symptoms or coronary involvement. In severe cases, tocilizumab and infliximab have been effective. Patients with hemodynamic instability and shock often require ventilation (21).

In 1401 (2022/2023), Shahbaznejad et al. conducted a cross-sectional study in Iran to investigate COVID-19 in children. The results showed that the prognosis of COVID-19 pneumonia in children was favorable if they had no underlying conditions. Although the disease is rare during the neonatal period, 3% of the hospitalized children were neonates, and 34% were under the age of 5. COVID-19 in children typically presents in two phases: respiratory symptoms in the first week, followed by MIS-C symptoms two to three weeks later (19). In 1400 (2021/2022), Mamishi et al. conducted a cross-sectional study in Tehran on MIS-C in children with COVID-19. The mean age was 7 years (ranging from 10 months to 17 years), with 53% being boys. Twenty-five patients had cardiac disease, and coronary artery dilation and myocarditis were observed in 31% and 18% of the patients, respectively. Renal failure occurred in 29% of cases. Twenty-seven patients (60%) were treated with methylprednisolone (dose range: 30 mg/kg/day), and 18 patients received IVIG (dose range: 2–4 g/kg). The mortality rate was 11%, with four of the deceased having underlying conditions (ALL, CKD, cerebral palsy, and Budd-Chiari syndrome), while no underlying disease was identified in the fifth deceased case (31).

In 2021, Cruz et al. conducted a cross-sectional study in the United States focusing on MIS-C cases related to COVID-19. Thirteen patients (87%) exhibited severe cardiac involvement, with abnormal echocardiography in 12 patients, elevated serum troponin or BNP in 13 patients, left ventricular dysfunction in 4, and biventricular dysfunction in 3 patients (26).

The study by Li et al., which aimed to investigate the epidemiological characteristics of COVID-19, analyzed 6,007 articles from 11 regions and countries. The average age of infected individuals was 46.7 years, with 51.8% being male. Among them, 22.9% experienced severe disease, and 5.6% had a fatal outcome. Underlying immunodeficiency, diabetes, and malignancy were linked to more severe illness, while male gender, older age, diabetes, and hypertension were associated with higher mortality. Gastrointestinal and respiratory symptoms were more common in severe cases, while pneumonia and end-organ failure were more frequent in those who died (32). In the study by Utku et al., 297 patients with COVID-19 were analyzed. The most common symptoms were cough (56.6%), fatigue and weakness (56.6%), taste disturbances (35.7%), and myalgia and fever (33).

According to another review study, the most common clinical symptoms in COVID-19 patients, in order, included fever, cough, fatigue, shortness of breath, diarrhea, dizziness, sore throat, and myalgia. COVID-19 is classified into three levels based on severity: mild, severe, and critical. Most patients experience mild symptoms and recover. Asymptomatic infections have also been reported; however, many of these asymptomatic patients eventually developed symptoms after identification (34).

A study conducted on COVID-19 patients found that

in severe cases, compared to mild ones, there was a significant reduction in lymphocytes, monocytes, and eosinophils, along with lower levels of hemoglobin and platelets. Additionally, low levels of albumin, serum sodium, and the lymphocyte-to-leukocyte ratio to CRP ratio were observed. Conversely, liver enzymes, bilirubin, blood urea, creatinine, inflammatory markers, fibrinogen, D-dimer, and the neutrophil-to-lymphocyte ratio all showed significant increases in patients with more severe disease (35).

Given the importance of investigating secondary complications of COVID-19, particularly in children, and in light of evidence pointing to MIS-C and cardiovascular complications following COVID-19 infection in children, as well as the limited number of studies in this area—especially in Iran and within the West Azerbaijan Province—the present study was designed to determine the prevalence of cardiac complications in children hospitalized with COVID-19 at Motahari Hospital in Urmia, the provincial pediatric referral center, during the years 2019–2021 (1398–1400 in the Iranian calendar).

Materials and Methods

This study was designed as a cross-sectional study. The study population consisted of children who were hospitalized with COVID-19 at Shahid Motahari Hospital in Urmia. The sampling method used was census-based, meaning all children diagnosed with COVID-19 and hospitalized at Shahid Motahari Hospital in Urmia between 2019 and 2021 were included. Inclusion criteria: Children under the age of 16 with a confirmed diagnosis of COVID-19 based on RT-PCR test results for COVID-19, performed on nasopharyngeal or oropharyngeal swabs. Exclusion criteria: Incomplete information or patients who voluntarily left the hospital before completing their treatment.

To collect data, a checklist was created based on the variables of interest, which was completed using the available information in the patients' medical records.

All records related to hospitalization for a COVID-19 diagnosis, as well as any subsequent admissions within two months from the previous COVID-19-related hospitalization, were reviewed for clinical symptoms, clinical signs, imaging findings, and cardiovascular evaluations. The findings from ECG and echocardiography reports, along with demographic, clinical, and paraclinical data, and the final outcomes of the patients, were recorded by the researcher in the checklist. The collected data were coded and entered into SPSS software version 27 for analysis in line with the study's objectives.

This study was conducted following ethical approval from the Ethics Committee of Urmia University of Medical Sciences, with approval number 11264.

Results

The results indicated that approximately 63.3% of the children were in the 1 to 5-year age group, 27.7% were under 1 year old, and 8% were between 5 and 15 years old. Of the children, 59.4% were male, and 40.6% were female. Around 53.4% of the children presented with general and systemic symptoms, 42.5% had predominantly

gastrointestinal symptoms, 33.6% had predominantly respiratory symptoms, and 14.8% experienced seizures following fever. The gastrointestinal symptoms included nausea, vomiting, diarrhea, and bloody diarrhea. Respiratory symptoms included cough and shortness of breath. Additionally, weakness, fatigue, fever, and body aches were considered systemic symptoms.

A chest CT scan was performed in 41.8% of the cases. Among these, 54 cases showed viral parenchymal changes in the lungs, 60 cases exhibited ground-glass opacities, and 28 cases had no significant changes in the lung parenchyma. Approximately 18.8% had a history of known cardiovascular issues. Additionally, 14.4% had a previous history of seizures or epilepsy. 9.8% had major neurological conditions, such as cerebral palsy and low IQ. Furthermore, 4.2% of the children had a history of various malignancies.

Table 1: Underlying Conditions in the Studied Children

Percentage	Frequency		
%62.9	122	Without a history of heart disease	Underlying diseases
%14.4	28	Epilepsy or seizures	
%3.1	6	Mazur surgeries	
%9.8	19	Major neurological problems	
%2.1	4	ITP	
%4.2	8	Malignancy	
%2.1	4	HRAD or Asthma	
%1.5	3	Metabolic disorders	
%18.8	26	Congenital heart diseases	

In total, among the hospitalizations related to a COVID-19 diagnosis and subsequent admissions shortly after the initial hospitalization, out of 194 children, an ECG was performed in 130 cases (67.0%) and was available for review. Additionally, echocardiography was conducted in 98 children (50.5%) during the hospitalization for COVID-19 or during subsequent hospitalizations for other reasons and was accessible. In contrast, 49.5% of the children, either during their COVID-19 hospitalization or subsequent admissions, had no clinical complaints or signs related to cardiovascular diseases, and echocardiography was not performed.

The majority of children had good ventricular function and a healthy ejection fraction (EF). Among the children with COVID-19, 18.8% had a known history of heart disease, and 10.8% of these children developed cardiac complications as a result of COVID-19. Additionally, 7.9% of children without a history of heart disease also developed cardiac complications. The frequency of the types of cardiac complications is illustrated in Figure 1. Other complications, each occurring in less than

10% of cases, included coronary artery aneurysm, MOD PI, mild dilation of the four heart chambers, dilation of the aortic root, decreased ejection fraction, mild AI, and severe PH.

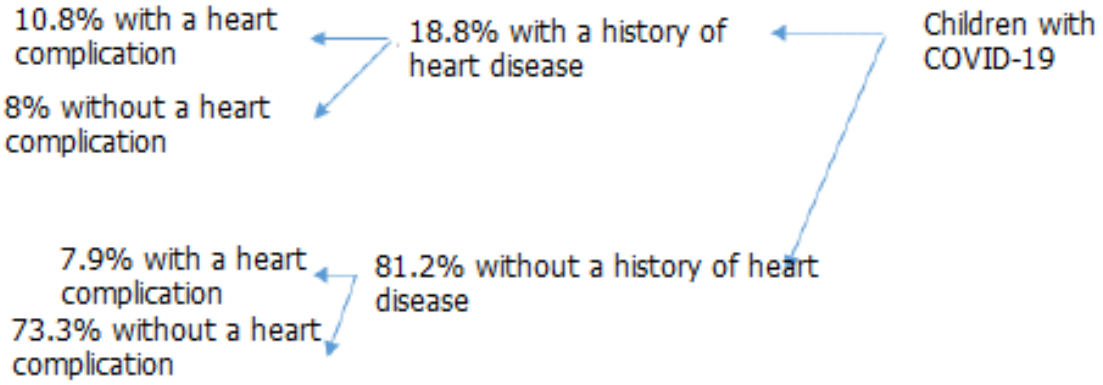

Figure 1: Frequency of Cardiac Complications in the Studied Children

Cardiac enzymes, including troponin and creatine kinase, were measured in 30 and 22 cases, respectively, of the total children studied. Of these, CTNI was positive in only 2 cases, while CKMB was positive in 4 cases. Among the 130 ECGs performed, 9 cases of bradycardia, 15 cases of tachycardia, and 6 cases of right axis deviation were reported. The remaining ECGs were normal, accounting for approximately 76%. Out of the 194 children studied, 10 died during hospitalization due to COVID-19, and 94.8% were discharged, as shown in Table 2.

Table 2: Hospital Outcome of the Children Studied

Hospital Outcomes	Death	(%5.2)10
	Discharge	(%94.8)184

Discussion

According to the findings of this study, 64.3% of children were in the 1 to 5-year age group, and approximately 59.4% of the hospitalized children with COVID-19 were male. In a study conducted in the United States by Moreira et al. (2021), which aligns with the present study, it was reported that most hospitalized children due to COVID-19 were in the 5 to 9-year age group, similar to our findings, with the next peak age group for hospitalization being 15 to 20 years. However, this age group was not included in our study. Contrary to the present study, the male-to-female ratio in their research was nearly equal, reported as 1:1 (36). A multicenter study by Rostami et al. (2022) also found that most hospitalized children with COVID-19, particularly those with MIS-C, were in the 1 to 5-year age group, with a slightly higher frequency of boys compared to girls (37). In Turkey, Ciftdogan et al. reported that most hospitalized children with COVID-19 were in the 3 to 7-year age group, but unlike our study, they found an equal gender ratio (38). In general, various studies have reported different demographic characteristics of children hospitalized with COVID-19 and those with MIS-C.

These differences may be attributed to factors such as the timing of the study (different peaks and variations of the virus), study methodologies, sampling techniques, and geographical differences. In children infected with COVID-19, the most common clinical symptoms include fever and cough, often accompanied by fatigue, myalgia, nasal congestion, runny nose, sneezing, sore throat, headache, dizziness, vomiting, and abdominal pain (39). A small number may be asymptomatic carriers, while others may present with unusual symptoms such as vomiting, diarrhea, and other gastrointestinal issues, or only asthma and shortness of breath. Additionally, studies have shown that initial respiratory symptoms can quickly progress to acute respiratory distress syndrome (ARDS) (40). One study reported that out of 134 children with the disease, 89 had a fever (41).

According to the findings of this study, children hospitalized with a diagnosis of COVID-19 exhibited general and systemic symptoms such as fever and myalgia, gastrointestinal symptoms including diarrhea and vomiting, and respiratory symptoms like cough and shortness of breath. Previous review studies have reported that cardiac involvement occurs in 67 to 80 percent of children with MIS-C, presenting as cardiac symptoms such as ventricular dysfunction, coronary artery aneurysm, conduction disorders, and arrhythmias (42, 43).

The clinical cardiac manifestations of COVID-19 can range across various severities. Many patients experience cardiovascular disorders and shock, which can be severe (44). However, some patients may present without any cardiovascular involvement. In this study, echocardiography results in children during subsequent hospitalizations after COVID-19 infection indicated that most pathological cases were due to congenital changes rather than the acute inflammatory process, with only 20% of children with COVID-19 developing cardiac complications. Among the children with COVID-19, 18.8% had a documented history of heart disease, including 36.8% with a patent foramen ovale (PFO), 31.5% with atrial septal defect (ASD) and patent ductus arteriosus (PDA), 21% with valve disorders, 15.7% with pulmonary hypertension, ventricular septal defect (VSD), 5% with coronary artery aneurysm, high blood pressure, ventricular hypertrophy, aortic valve replacement surgery, tetralogy of Fallot, cardiomyopathy, and dextrocardia. Of the children with a history of heart disease, 10% developed cardiac complications, most commonly tricuspid and pulmonary valve insufficiency, mitral valve insufficiency, and pleural effusion. In the ECG analysis, apart from tachycardia and right-axis deviation, no other pathological findings or arrhythmias were observed. However, the retrospective nature of the study, the lack of precise follow-up of the children, and the limited assessment of their cardiac manifestations are limitations that affect the study's results. Similar to the present study, other research has shown that functional recovery and outcomes of coronary

arteries in children with multisystem inflammatory syndrome (MIS-C) are generally positive. For example, a study by Matsubara et al. (2021) in the USA demonstrated that all pathological changes observed during the acute phase of MIS-C resolved completely within a short period (45). A study in Turkey did not report significant changes in the cardiovascular system during the inflammatory phase of MIS-C (38). In a multicenter study by Memishi et al., only minor coronary artery changes, such as dilation, were observed, and no major cardiovascular changes were noted during the acute MIS-C phase (46).

Conclusion

The results of the present study indicated that cardiovascular involvement in children with COVID-19 was not highly prevalent, and the changes observed during the acute inflammatory process, including multisystem involvement such as MIS-C, were generally transient and reversible.

It is recommended that future studies with larger sample sizes, multicenter approaches, and more precise follow-up of children be conducted to gather more comprehensive data on cardiovascular manifestations in COVID-19 cases and its secondary complications, such as MIS-C.

One limitation of this research was the lack of access to necessary information for some patients, as well as the retrospective, case-file-based nature of the study, which resulted in the loss of more detailed clinical data.

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