Echocardiographic Findings in Pediatric Patients with COVID-19

BY

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ABSTRACT

Background: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) a novel coronavirus causing COVID-19 was identified in December 2019, The virus spread around the whole world in a short time and World Health Organization(WHO) declared the pandemic status by 11 March 2020.

Aim and objectives: to investigate echocardiographic abnormalities in pediatric patients with COVID-19. Also, the study aims to correlate the clinical and laboratory data with echocardiographic findings.

Subjects and methods: this retrospective study was conducted in Pediatric Department and PICU of Minia Insurance Hospital, Minia, Egypt. The study included 60 children divided into 3 groups; pneumonia, MIS-C and control; each had 20 children. The duration of the study ranged from 6-12 months.

Results: there was a statistically significant difference between the studied groups regarding Presentation distribution, Echocardiographic parameters except in septal mitral e′ and Lateral/septal e′ ratio. There was no statistically significant difference between the studied groups regarding Demographic characteristics, Comorbidities distribution and Clinical course except in Myocarditis.

Conclusion: the most common echocardiographic findings in MIS-C patients is right ventricular dysfunction. However, mid- and long-term follow-up studies are needed for both coronary artery involvement and left ventricular diastolic dysfunction in MIS-C patients.

Keywords: SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2); Pediatric; COVID-19.

INTRODUCTION

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) a novelcoronavirus causing COVID-19 was identified in December 2019.[1] The virus spread around the whole world in a short time and World Health Organization (WHO) declared the pandemic status by 11 March 2020.[2]

The COVID-19 symptoms seem to be less severe in children than in adults. The symptoms are typical of acute respiratory infections included tachypnoea, tachycardia, fever, cough, sore throat, pharyngeal erythema, sneezing, rhinorrhea, myalgia, fatigue and wheezy chest. The less commonly presented symptoms and signs are diarrhea, vomiting, low oxygen saturations of less than 92%.[3,4]

It is now known that many patients who recover from the acute phase of the Coronavirus disease 2019 (COVID-19) continue to have clinical manifestations or develop new ones. This finding has alerted the scientific community, and researchers immediately began investigating these alterations and the possible correlation with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[5]

Ongoing symptomatic COVID-19 and post COVID-19 syndrome are referred to as long COVID 4 but the term post COVID-19 condition is also used.[6]

A significant proportion of children with MIS-C have cardiovascular manifestations in the form of myocardial dysfunction, shock, coronary artery dilatation and aneurysms, pericardial effusion, and rhythm disturbances.[7-9]

Conventional echocardiography is essential for a rapid evaluation of the cardiac function in children with MIS-C. Acute cardiac failure in patients with MIS-C is frequent (80–85% of cases) and is the major determinant of severity.[10]

Conventional echocardiography, including left ventricle ejection fraction, mitral inflow velocities by spectral Doppler, tricuspid annular plane systolic excursion by M-Mode, and lateral mitral/tricuspid peak velocities on tissue Doppler, are useful to diagnose cardiac dysfunction, guide clinical decisions (fluid therapy, inotropic/mechanical circulatory support), monitor treatment response, and support follow-up programs in children with MIS-C.[11]

The aim of this study was to investigate echocardiographic abnormalities in pediatric patients with COVID-19. And to correlate clinical and laboratory data with echocardiographic findings.

PATIENTS AND METHODS

Ethical Considerations: Written informed consent was obtained from all guardians of the included participants in the study. The study was approved by Ethics Committee of Faculty of Medicine, Al- Azhar University. Adequate provisions to maintain the privacy of participants and confidentiality of the data are as the following: We hide the name of patient in the research and put a code number to every patient's name and address that was kept in a special file and We used the results of the research only in scientific aim and not use it in any other aim.

Inclusion Criteria: Children aged 1 month to 18 years of both sex, History of confirmed (nasopharyngeal swab) SARS-CoV-2 infection or subsequent seroconversion, Acute phase of COVID-19 during 1–6 months before enrollment in the study and.

Exclusion criteria: Children with previously diagnosed cardiac abnormalities or cardiac dysfunction, Diagnosed co-infections and COVID-19 onset more than 6 months previously.

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA).

Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data.

One-way ANOVA test was used to compare between more than two dependent groups of normally distributed variables. While Kruskal-Wallis test was used for non-normally distributed variables.

Repeated measures ANOVA test was used to compares means across one or more variables that are based on repeated observations of normally distributed variables. While Friedman test was used for non-normally distributed variables.

All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, $p < 0.001$ indicates highly significant difference while, $P > 0.05$ indicates Non-significant difference.

This retrospective study was conducted in Pediatric Department and PICU of Minia Insurance Hospital, Minia, Egypt. The study included 60 children divided into 3 groups; pneumonia, MIS-C and control; each has 20 children. The duration of the study ranged from 6-12 months.

This study included 60 children that divided into three groups: (Group 1) 20 children diagnosed with COVID-19 pneumonia, (Group 2) 20 children with of MIS-C was made according to U.S. Centers for Disease Control and Prevention (CDC) criteria and (Group 3) 20 children without pneumonia served as control.

Sample size: The sample size was calculated using the Epi Info program developed by Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia (US) version7 software, based on the following findings: a previous study reported that 48% of the included children with COVID-19 infection showed echocardiographic abnormalities.[12]

Thus, it was estimated that a minimal sample size of 60 children is required to achieve a power of 80% to detect an expected difference in the prevalence of abnormal echocardiographic findings of 10% at a significance level of 0.05.

Detailed methodology

The following data for each participant in the study was collected as follows (based on the review of medical records and echocardiogram reports): History, Physical symptoms, Laboratory parameters, Radiology, Echocardiography and Outcomes.

RESULTS

Table (1): Demographic characteristics among the studied groups

		Pneumonia (n=20)	**MIS-C** (n=20)	**Control** (n=20)	F	**P**
Age (years) Mean ± SD		11.45 ± 2.99	10.28 ± 2.61	10.76 ± 2.38	0.969	0.386
Gender	Female	8 (40%)	9 (45%)	10 (50%)	x^2 0.404	0.817
	Male	12 (60%)	11 (55%)	10 (50%)		
BMI (kg/m^2) Mean ± SD		21.39 ± 2.78	19.79 ± 2.14	20.44 ± 2.55	2.100	0.136
Residence	Urban	9 (45%)	8 (40%)	10 (50%)	x^2 0.404	0.817
	Rural	11 (55%)	12 (60%)	10 (50%)		

BMI: body mass index.

This table shows that there is no significant difference between the groups regarding age, gender, residence and BMI.

Table (2): Comorbidities distribution among the studied groups.

	Pneumonia (n=20)		**MIS-C** (n=20)		**Control** (n=20)		**P**
	N	%	N	%	N	%	
Obesity	5	25%	2	10%	4	20%	0.459
Asthma	3	15%	2	10%	2	10%	0.851
Diabetes mellitus	1	5%	0	--	0	--	0.362
Autoimmune disease	1	5%	1	5%	0	--	0.596
History of COVID-19 exposure	13	65%	7	35%	6	30%	0.054

This table shows that there is no significant difference between the groups regarding comorbidities and history of COVID-19 exposure.

Table (3): Presentation distribution among the studied groups.

	Pneumonia (n=20)		**MIS-C** (n=20)		**Control** (n=20)		**P**
	N	%	N	%	N	%	
Fever	17	85%	20	100%	12	60%	**0.004**
Cough	11	55%	7	35%	1	5%	**0.003**
Shortness of breath	10	50%	1	5%	0	--	**<0.001**
Nausea & vomiting	6	30%	14	70%	2	10%	**0.001**
Diarrhea	3	15%	10	50%	2	10%	**0.006**
Abdominal pain	1	5%	11	55%	0	--	**<0.001**
Rash	0	--	7	35%	0	--	**<0.001**

This table shows that there is a significant higher respiratory symptoms including cough and shortening of breath in COVID infected patients especially those with COVID pneumonia and significant extra-respiratory manifestations in in COVID infected patients especially those with MIS-C.

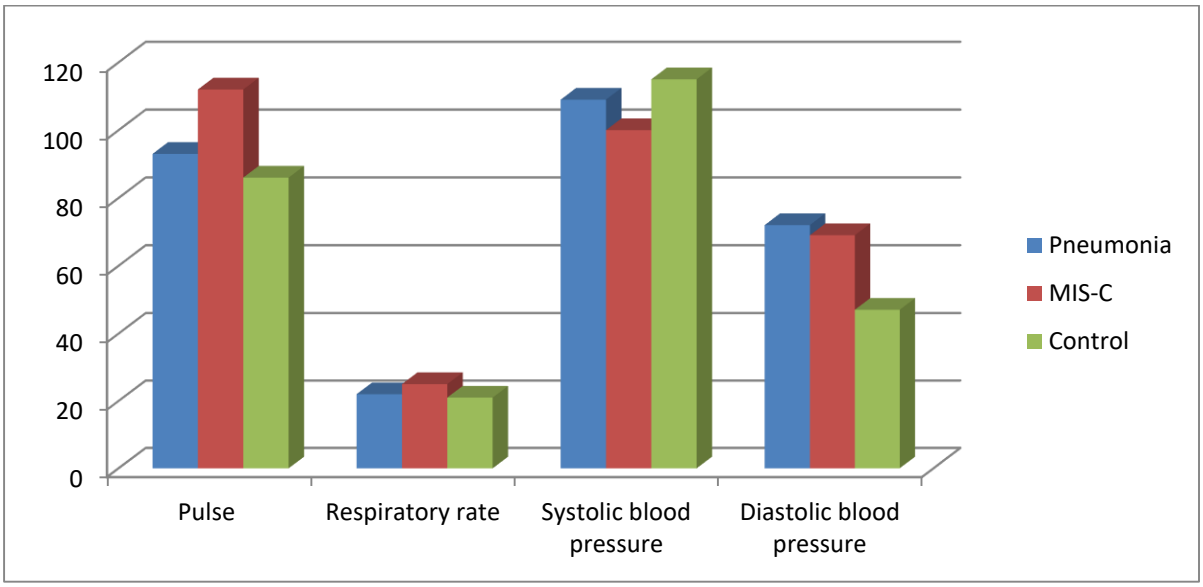

Figure 1: vital data among the studied groups

Table (4): Echocardiographic parameters of the three groups.

	Pneumonia (n=20)	**MIS-C** (n=20)	**Control** (n=20)	**F**	**P**
Ejection fraction (%) Mean ± SD	55.97 ± 11.63	49.25 ± 8.11	62.13 ± 3.88	**3.23**	**.047**
Fractional shortening (%) Mean ± SD	33.5 ± 4.05	30.91 ± 6.78	38.74 ± 4.15	**9.89**	**.001**

E/A ratio Mean ± SD	1.31 ± 0.642	1.47 ± 0.531	2.17 ± 0.341	**15**	**<0.001**
TAPSE (mm) Mean ± SD	21.17 ± 6.73	20.34 ± 5.86	25.49 ± 4.73	**7.12**	**.001**
Coronary diameter (mm) Mean ± SD	3.15 ± 0.31	3.70 ± 0.93	3.08 ± 0.27	**6.69**	**0.002**
PULMONARY PREESURE	55.97 ± 11.63	49.25 ± 8.11	62.13 ± 3.88	**3.23**	**.047**

TAPSE: tricuspid annular plane systolic excursion.

This table shows that there is a significant impaired echocardiographic parameters including EF, FS, E/A ratio, Lateral mitral e′, E/e′ ratio, and TAPSE, PULMONARY PREESURE and more coronary dilatation in among MIS-C patients compared to pneumonia groups and control group.

Table (5): Clinical course among the studied groups

	Pneumonia (n=20)		**MIS-C** (n=20)		**Control** (n=20)		
	N	%	N	%	N	%	
Pericardial effusion	4	20%	7	35%	0	0%	0.289
Pleural effusion	13	65%	8	40%	0	0%	0.113
Pericarditis	2	10%	6	30%	0	0%	0.114
Myocarditis	3	15%	9	45%	0	0%	0.001*

Regarding clinical course of our studied COVID infected population, there was statistically significant higher incidence of myocarditis in MIS-C patients than COVID pneumonia patients (45% vs 15%).

Despite higher in pleural effusion (65% vs 40%) in COVID pneumonia patients than MIS-C patients and higher pericardial effusion (35% vs 20%), pericarditis (30% vs 10%) in MIS-C patients than COVID pneumonia patients but the difference between both groups was statistically insignificant.

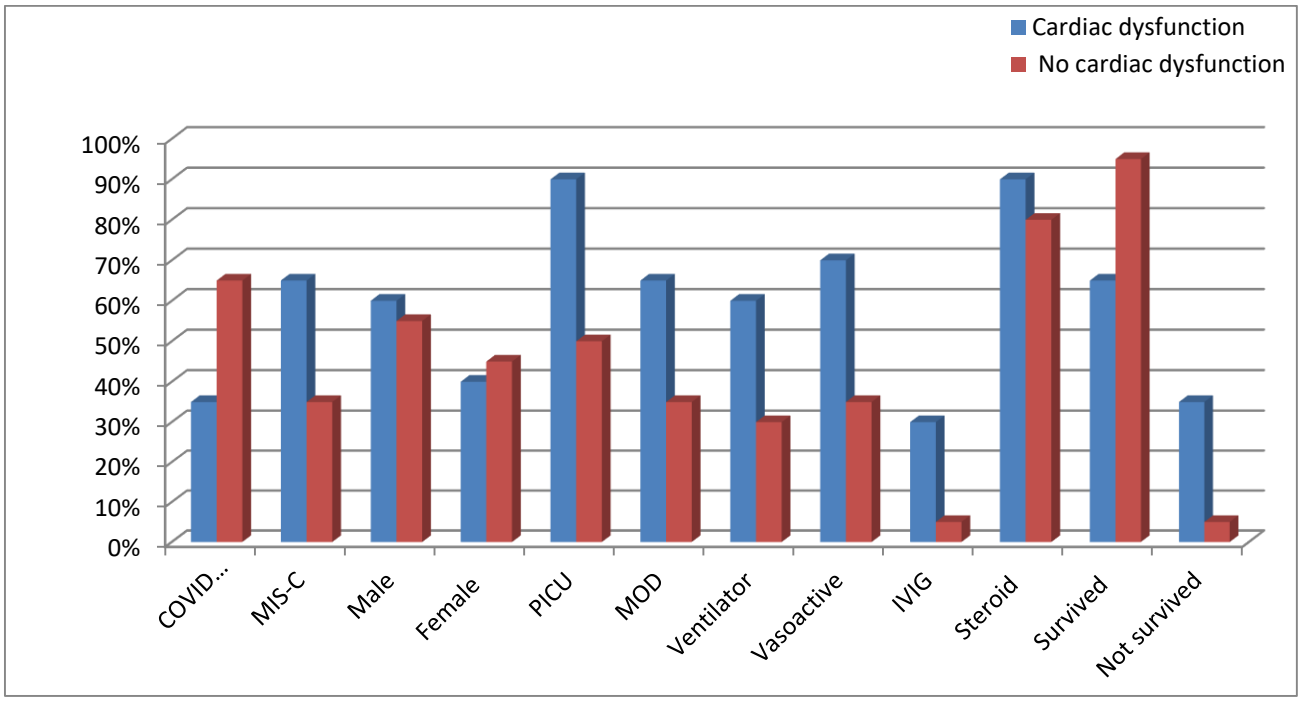

Figure 3: outcome in relation to cardiac function

DISCUSSION

The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has infected individuals of all ages in nearly every country on Earth. In Europe, Italy was the first country to be affected significantly by the outbreak of COVID-19, which began there in February 2020. From the Bergamo province, the epicenter of the Italian outbreak, Verdoni et al. first reported an exceedingly high number of Kawasaki disease (KD)–like cases starting in March 2020, with a monthly incidence that greatly exceeded the monthly incidence of the previous 5 years. Moreover, there was a clear starting point after the first case of COVID-19 was diagnosed in the Italian epicenter.[13]

The main results of this study were as following:

There is no significant difference between the groups regarding age, gender, residence and BMI.

Our results were in agreement with study of Kavurt et al. as they included 50 MIS-C patients and age-matched 40 healthy controls. The patients and controls were similar in terms of age, gender, body weight, body mass index (BMI), and body surface area (BSA).[14]

However, in the study of Matsubara et al, a total of 28 MIS-C patients were included in this study. Compared with KD patients, MIS-C patients were significantly older (median age: 11.4 years vs. 3.1 years; $p < 0.01$) and had larger statures (median body mass index: 22.5 kg/m2 vs. 16.0 kg/m2; $p < 0.01$). In total, 50% of MIS-C patients were considered

obese based on the World Health Organization definition. There was no sex difference in MIS-C patients.[11]

The present study showed that there is no significant difference between the groups regarding comorbidities and history of COVID-19 exposure. There there is a significant higher respiratory symptoms including cough and shortening of breath in COVID infected patients especially those with COVID pneumonia and significant extra-respiratory manifestations in in COVID infected patients especially those with MIS presentation.

While, in the study of Dufort et al. a total of 191 potential cases were reported. Of 95 patients with confirmed MIS-C (laboratory-confirmed acute or recent severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection and 4 with suspected MIS-C (met clinical and epidemiologic criteria). All the patients had fever or chills at admission. Other common presenting symptoms were gastrointestinal (80%), dermatologic (62%), mucocutaneous (61%), and lower respiratory (40%).[7]

The current study showed that there is a significant higher pulse, respiratory rate and lower systolic blood pressure and diastolic blood pressure in among MIS-C patients compared to pneumonia groups and control group suggesting higher hemodynamic instability in COVID infected patients especially those who developed MIS-C.

Our results were supported by study of Kavurt et al. as they reported that heart rate was significantly higher ($p < 0.001$), systolic and diastolic blood pressure were significantly lower in the MIS-C group compared to controls ($p < 0.05$).[14]

Our results showed that as regard echo; there is a significant impaired echocardiographic parameters including EF, FS, E/A ratio, Lateral mitral e′, E/e′ ratio, and TAPSE and more coronary dilatation in among MIS-C patients compared to pneumonia groups and control group.

Left ventricular dysfunction was significantly more frequent among MIS-C (30%) and pneumonia groups (35%) compared to control group (0%). Furthermore, severe left ventricular dysfunction was significantly more frequent among MIS-C (30%) compared to pneumonia groups (5%) and control group (0%) suggesting worse cardiac function in MIS-C patients.

Despite higher right ventricular dysfunction among MIS-C (10%) and pneumonia groups (5%) compared to control group (0%) but the difference was statistically insignificant. Coronary dilatation was significantly more frequent among MIS-C (20%) compared to pneumonia groups (0%) control group (0%). There is a significant difference between the groups regarding left ventricular.

Our results were supported by study of Kavurt et al. as they reported that on the day of worst left ventricular (LV) systolic function (echo-1), all left and right ventricular systolic function parameters were significantly lower ($p < 0.001$), E/A ratio was significantly lower, and averaged E/e′ ratio was significantly higher (median 1.5 vs. 1.8, $p < 0.05$; 8.9 vs. 6.3, $p < 0.001$ respectively) in patients compared to control. Patients were divided into 2 groups according to 3D LV ejection fraction (LVEF) on the echo-1: Group 1;

LVEF < 55%, 26 patients, and group 2; LVEF ≥ 55%, 24 patients. E/e′ ratio was significantly higher in group 1 than group 2 and control at discharge (median 7.4 vs. 6.9, p = 0.005; 7.4 vs. 6.3, p < 0.001 respectively).[14] Also, Valverde et al. reported pericardial effusion with a rate of 27.9% and MR with a rate of 42.5% in a large European cohort.[15]

An adult study from the Wuhan cohort concluded that myocardial damage contributed to 40% of SARS-CoV-2 deaths.[16] The incidence of myocarditis in 112 COVID-19 patients from Wuhan, China, diagnosed by elevated Troponin-I (>0.12 ng/ml), abnormalities on standard echocardiograms, and/or electrocardiograms was 12.5%.[17]

Moreover, Erol et al. revealed that statistically significant differences were found in left ventricular ejection fraction, relative wall thickness, and tricuspid annular plane systolic excursion.

In current study, regarding clinical course of our studied COVID infected population, there was statistically significant higher incidence of myocarditis in MIS-C patients than COVID pneumonia patients (45% vs 15%). Despite higher in pleural effusion (65% vs 40%) in COVID pneumonia patients than MIS-C patients and higher pericardial effusion (35% vs 20%), pericarditis (30% vs 10%) in MIS-C patients than COVID pneumonia patients but the difference between both groups was statistically insignificant.[18]

Our results agreement with Matsubara et al. who found that MIS-C patients with myocardial injury were more affected than those without myocardial injury with respect to all functional parameters. The strongest parameter to predict myocardial injury in MIS-C were global longitudinal strain, global circumferential strain, peak left atrial strain ,and peak longitudinal strain of right ventricular free wall . Compared with the classic KD group, MIS-C patients had more mitral regurgitation (MR) (46% vs.15%; p¼0.06), more pericardial effusion (32%vs. 15%; p¼0.46).[11]

This study has some limitations. This was a single-center, prospective study with enough sample size. However, we are aware that MIS-C is a novel disease and our study has some limitations. One of the limitations of the study was the acquisition of three-dimensional echocardiographic images, especially in children < 5 years old.

CONCLUSION

Our results showed that the most common echocardiographic findings in MIS-C patients is left ventricular dysfunction. However, mid- and long-term follow-up studies are needed for both coronary artery involvement and left ventricular diastolic dysfunction in MIS-C patients.

RECOMMENDATION

Early treatment and diagnosis prevent the development of cardiac dysfunction &pulmonary hypertension in children

LIMITATIONS

1. Sample size is relatively not large.
2. To date, only a handful of non-randomized studies exist to support the effectiveness.

REFERANCES

1. Guan W-j, Ni Z-y, Hu Y, et al., 2019 Clinical characteristics of coronavirus disease in China. *New England journal of medicine*.;382(18):1708-1720.
2. Di Gennaro F, Pizzol D, Marotta C, et al. 2020, Coronavirus diseases (COVID-19) current status and future perspectives: a narrative review. *International journal of environmental research and public health*.;17(8):2690.
3. Eastin C, Eastin T. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China: Dong Y, Mo X, Hu Y, et al. Pediatrics. . 2020, *Journal of Emergency Medicine*. 2020;58(4):712-713.
4. Lu X, Xiang Y, Du H, Wing-Kin Wong G. 2020, SARS-CoV-2 infection in children–Understanding the immune responses and controlling the pandemic. *Pediatric Allergy and Immunology*.;31(5):449-453.
5. Nalbandian A, Sehgal K, Gupta A, et al. 2021, Post-acute COVID-19 syndrome. *Nature medicine*.;27(4):601-615.
6. Stephenson T, Pereira SMP, Shafran R, et al2022. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCk): a national matched cohort study. *The Lancet Child & Adolescent Health*.;6(4):230-239.
7. Dufort EM, Koumans EH, Chow EJ, et al2020. Multisystem inflammatory syndrome in children in New York State. *New England Journal of Medicine*.;383(4):347-358.
8. Hoste L, Van Paemel R, Haerynck F. Multisystem inflammatory syndrome in children related to COVID-19 2021: a systematic review. *European journal of pediatrics*.;180:2019-2034.
9. Williams V, Dash N, Suthar R, et al2020. Clinicolaboratory profile, treatment, intensive care needs, and outcome of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2: a systematic review and meta-analysis. *Journal of Pediatric Intensive Care*.;11(01):001-012.
10. Alsaied T, Tremoulet AH, Burns JC, et al2021. Review of cardiac involvement in multisystem inflammatory syndrome in children. *Circulation*.;143(1):78-88.
11. Matsubara D, Kauffman HL, Wang Y, et al. 2020 Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. *Journal of the American College of Cardiology*.;76(17):1947-1961.
12. Diniz MdFR, Cardoso MF, Sawamura KSS, et al. The heart of pediatric patients with COVID-19: 2021 new insights from a systematic echocardiographic study in a tertiary hospital in Brazil. *Arquivos Brasileiros de Cardiologia*.;117:954-964.
13. Verdoni L, Mazza A, Gervasoni A, et al 2020. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet*.;395(10239):1771-1778.
14. Kavurt AV, Bağrul D, Gül AEK, et al 2022. Echocardiographic findings and correlation with laboratory values in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. *Pediatric cardiology*.:1-13.

15. Valverde I, Singh Y, Sanchez-de-Toledo J, et al 2021. AEPC COVID-19 Rapid Response Team*. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. *Circulation*.;143(1):21-32.

16. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 2020 based on an analysis of data of 150 patients from Wuhan, China. *Intensive care medicine*.;46(5):846-848.

17. Deng W, Bao L, Liu J, et al. 2020 Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. *Science*.;369(6505):818-823.

18. Erol N, Alpinar A, Erol C, Sari E, Alkan K. Intriguing new faces of Covid-19: 2022 persisting clinical symptoms and cardiac effects in children. *Cardiology in the Young*.;32(7):1085-1091.