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Original Research

Comparison of Cardiac Findings in Pediatric Patients with Multisystem Inflammatory Syndrome in Children Associated with COVID-19

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Abstract

Objectives: Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious hyperinflammatory complication of COVID-19 in which cardiovascular abnormalities are frequently detected. In the context of MIS-C, it remains uncertain which patients will develop cardiac dysfunction and which will experience coronary artery abnormalities (CAAs). To investigate this, patients were categorized into four distinct groups based on the presence or absence of myocardial dysfunction and/or CAAs. We aimed to determine whether there were any differences in demographic, echocardiographic, laboratory results, outcome, and COVID-19 variants between the groups.

Methods: Between July 2020 and August 2022, 135 MIS-C diagnosed patients were divided into 4 groups according to their cardiovascular involvement.

Results: The mean age of the patients was 104 months (9-209 months) and the male/female ratio was 1.45. Thirty-eight percent of the patients had decreased LVEF and 44% had signs of CAAs. Fifty-nine percent (80/135) of the patients were admitted to the pediatric intensive care unit (PICU). Patients admitted to the PICU were older patients with cardiac dysfunction. The severity of cardiac involvement ranged from severe to mild in Group 1, Group 2, Group 3, and Group 4, respectively. Group 1 was older (median age 146 months, p=0.008), albumin was lower (p=0.015) and CRP was higher than Group 4 (p=0.007). PICU admission/stay time and CRP elevation were significant in the groups with decreased LVEF (groups 1 and 2). More MIS-C patients were observed in the alpha wave compared to other waves, but there was no difference in the severity of cardiac involvement (p=0.25). Cardiac dysfunction and improvement in CAAs were observed in patients. The case fatality rate was 1.48%.

Conclusion: D-dimer, CRP, ferritin levels were higher, lymphocyte, platelet and albumin levels were lower in elderly patients with cardiac dysfunction who were followed up in the PICU.

Keywords: Coronary artery abnormalities (CAAs), decreased LVEF, MIS-C, PICU, SARS CoV-2 variants

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SARS-CoV-2, which was detected in 2019 and caused the COVID-19, became a global pandemic in 2020. First reports speculated that children were experiencing a mild COVID-19 infection. But, the UK reported pediatric cases similar to Kawasaki Disease (KD) or toxic shock syndrome in April 2020. Later, a new pediatric disease was identified, multisystem hyperinflammatory syndrome (MIS-C), presenting with fever, hypotension, gastrointestinal symptoms, and myocardial dysfunction. Children who have MIS-C also have cardiac involvement, including left ventricular dysfunction, coronary artery abnormalities (CAAs), pericardial effusion, arrhythmias, and conduction abnormalities. The most frequent systemic involvement of MIS-C patients (cardiac involvement) plays an important roles in prognosis-treatment with a rate of 50-95%. [1-6] In many case series, reduced left ventricular function in the early phase of the disease has been reported in 30-40% and CAAs in 8-24%.[7-11]

SARS-CoV-2 underwent mutations during the pandemic that altered infectivity, transmission, and severity. Previous studies report that acute Omicron variant infection had less severe clinical manifestation, but Delta caused more severe progression. Results regarding other variants such as Alpha, Beta, and Gamma are more limited. Some studies have suggested that these variants did not alter the clinical presentation of MIS-C or that they had similar severity and prevalence compared to previous variants. Some studies speculated an effect on the presentation and severity of MIS-C, but others reported no differences.[12-14] Discussions regarding the effects of variants on pediatric MIS-C continue, and more data and long-term studies are needed to reach a definitive conclusion.

KD is an acute-onset systemic vasculitis involving small and medium-sized arteries. Cardiac manifestations may include CAAs and myocarditis. Approximately 80% of KD occurs in pediatric patients under 5 years of age. The pathogenesis of KD has not been fully defined; but, infections caused by environmental and genetic factors may be the trigger of the disease. The similar clinical course of KD and MIS-C causes difficulties in the differentiation of both conditions. MIS-C especially affects school-age children. The median age is reported to be approximately 8.3 years and it is more frequent in males.[15] It remains unclear which patient will develop cardiac dysfunction and which patient will develop CAAs. In the present study, patients were divided into four groups according to the presence or absence of myocardial dysfunction and/or CAAs. We aimed to determine whether there was a difference in demographic, echocardiographic, laboratory results, outcome, and COVID-19 variants between the groups.

Methods

Study Sample

The data of 135 MIS-C patients (July 2020 - August 2022) are reported in this retrospective case study. We specifically focused on cardiovascular involvement in MIS-C. Patients who met the following criteria were included in the study.

1. Patients who met the criteria of the Centers for Disease Control and Prevention (CDC) for MIS-C diagnosis[16]
2. Patients who had no previous cardiovascular comorbidities (including congenital heart defects such as atrial septal defects, ventricular septal defects, patent ductus arteriosus, and tetralogy of Fallot, or acquired conditions like hypertension or valvular heart disease)
3. Children <18 years of age with at least one echocardiographic (echo) result available

Exclusion criteria include children over the age of 18.

Echocardiography

Transthoracic 2D echocardiograms with Doppler Ultrasonography were performed on all patients by pediatric cardiologists with a Phillips IE33, Epiq 7C (Philips Medical Systems, Andover, MA), or GE VIVID E95 (GE Healthcare, Chicago, IL) at the time of diagnosis and when clinically indicated. Ejection fraction, Tricuspid Annular Plane Systolic Excursion (TAPSE), Mitral Annular Plane Systolic Excursion (MAPSE), coronary artery dimensions, qualitative degrees of valve insufficiency, and pericardial effusion size were recorded.

MAPSE, TAPSE and z-scores were used to assess ventricular longitudinal function.[17,18]

Study Design and Definitions

Left Ventricular Ejection Fraction (LVEF) was defined as normal (LVEF≥55%) or reduced (LVEF<55%).[17] CASs were defined and classified according to the American Heart Association Guideline (dilation; z score 2 to <2.5, small aneurysm; z score≥2.5 to 5, moderate aneurysm; z score≥5 to <10, large or giant aneurysm: z score≥10).[19] "Perivascular brightness/echogenicity" was used to define an abnormal coronary that did not meet the criteria for dilation or aneurysm.[9,20]

Patients were divided into four groups based on cardiac involvement:

Group 1; CAAs in combination with decreased LVEF

Group 2; Coronaries normal but decreased LVEF

Group 3; Normal LVEF with CAAs (perivascular brightness/echogenicity, z score <2)

Group 4; Normal coronaries and LVEF (Valvar dysfunction and/or minimal pericardial effusion may be present)

The World Health Organization categorized SARS-CoV-2 variants into three groups as variants of concern (VOC), variants under surveillance (VUM), and variants requiring consideration (VOI). Following the Alpha (B.1.1.7) variant, which was first identified in December 2020, Beta (B.1.351), Gamma (P1), Delta (B.1.617.2), and the Omicron (B.1.1.529) variant, which is closely monitored recently, have been identified as the main variants of concern.[21] In our country, as in the rest of the world, three main waves of increasing case numbers were identified. Following the first wave caused by the Alpha Variant that started in December 2020, the second wave occurred in May 2021 with the Delta Variant, and the third wave in December 2021 with the Omicron Variant. There has been no increase in the number of cases because of the Beta and Gamma variants in our country.

Demographic data, ward/intensive care length of stay, and mortality were recorded. Laboratory results (White blood cell (WBC), red blood cell (RBC), hemoglobin (Hgb), platelet count (PLT), neutrophil count, lymphocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], albumin), interleukin-6 (IL-6), N-terminal prohormone B-type natriuretic (Pro-BNP), Troponin I, and D-dimer results were obtained from hospital records.

Statistical Analysis

The SPSS software 25.0 (IBM Inc., Chicago, IL) was used for statistical analyses. To determine whether the data was normally distributed, The Shapiro–Wilk test was used. The groups were compared using one-way ANOVA or the Kruskal-Wallis H test, as appropriate. Following these analyses, the significant groups were compared using Tukey's HSD multiple range test or the Mann-Whitney U test (Bonferroni correction was used for which adjusted alpha value (4C2=0.05/6 =0.008)). The findings were presented as mean SD or median (min-max) and $p<0.05$ was taken statistical significance.

The study was conducted in accordance with the Declaration of Helsinki.

Approval for the study was obtained from the study was approved by the Ankara Bilkent City Hospital Medical Research Scientific and Ethics Review Committee (date: 29.05.2024, number: TABED 2-24-190).

Results

The median age of the patients was 104 months (9-209 months) and 59.2% were male. Median test results are as follows: Troponin I 23 ng/L (2-10810 ng/L), Pro-BNP 2000 ng/L (17-35000 ng/L), D-Dimer 2.4 mg/L (0.26-35.2 mg/L), ferritin 250 ug/L (29-10690 ug/L), ESR 47 mm/h (3-132 mm/h), CRP 150 mg/L (5-340 mg/L), procalcitonin 1.7 ug/L (0.03-116 ug/L), IL-6 65.9 pg/mL (2-11328 pg/mL). Thirty-eight percent of patients had decreased LVEF and 44% had evidence of CAAs (10% coronary artery dilatation and/or aneurysm, 34% prominent).

Fifty-nine percent (80/135) of the patients were admitted to the pediatric intensive care unit (PICU). Patients admitted to PICU were older patients with cardiac dysfunction and had higher levels of D-dimer, CRP, ferritin, and lower levels of lymphocytes, platelets, and albumin among laboratory parameters (Table 1).

Patients were divided into four groups according to the severity of cardiac involvement. Demographic, echocardiographic, laboratory, and mortality results of the patients according to the groups are presented in Table 2. The severity of cardiac involvement was Group 1, Group 2, Group 3, and Group 4 from severe to mild, respectively.

Group 1 was statistically older than Group 4 (median age 146 months, p=0.008). Additional analysis was performed to understand the reason for the difference. The 15 patients (LVEF <%55 with prominent CAAs) in Group 1 were older in median age compared to the patients in Group 3 (median age 158 months, p=0.003). Older children appear to be more likely to develop cardiac dysfunction. In Group 1, albumin was statistically lower and CRP was higher compared to Group 4 (p=0.015, p=0.007). Admission to the intensive care unit, length of stay in the intensive care unit, and CRP elevation were statistically significant in the groups with decreased LVEF (Group 1, Group 2) compared to Group 4.

Valvar dysfunction was detected in approximately 33% of patients. The mitral valve was the most commonly affected in 26%. Echocardiographic small pericardial effusion was detected in 9.6% of patients.

Arrhythmias and electrocardiographic changes were detected in 37.7% of patients. The most frequent non-specific ST and T wave changes and grade 1 atrioventricular block were detected.

CAAs were found in 10% of children (10 dilatation, 6 small aneurysm, 1 medium aneurysm). Right coronary artery (RCA) and left main coronary artery (LMCA) involvement was equal. The least affected coronary artery was the left anterior descending (LAD) (Fig.1).

During the alpha wave, more MIS-C patients were followed up compared to the other waves, and no difference was

Table 1. Comparison of Clinical Characteristic of İntensive Care Patients

Variables	Service (n=55)	PICU (n=80)	P
Age, months	84 (9-200)	125 (18-209)	**<0.001**#
Male	29 (52.7%)	51 (63.7%)	0.200Θ
LVEF (%)	66.11±5.11	56.30±10.47	**<0.001**Θ
LVFS (%)	35.40±4.25	29.15±7.14	**<0.001**Θ
MAPSE (mm)	11.97±2.39	11.10±2.58	0.103Θ
TAPSE (mm)	18.63±3.86	18.90±3.78	0.729Θ
Pro-BNP ng/L (reference range <125 ng/L)	858 (17-35000)	2000 (17-35000)	**<0.001**#
Troponin ng/L (reference range <45 ng/L)	4 (2-580)	23 (2-10810)	**<0.001**#
WBC (10^3/µL) (reference range 4.0–10.0 10^3/µL)	8700 (2600-26100)	9190 (1100-37000)	0.513#
Absolute neutrophil count (10^3/µL)	6500 (1230-22700)	7280 (11-33600)	0.329#
Absolute lymphocyte count (10^3/µL)	1100 (360-5500)	930 (210-3900)	**0.046**#
Hb (g/dL) (12.0–16.0)	12.40±1,37	11.77±1.96	0.041Θ
Platelets (10^3/µL) (reference range 130–450 10^3/µL)	244000 (60000-550000)	188500 (43000-517000)	**0.002**#
Na (mEq/L) reference range 132-146 mEq/L)	134.6±3.3	134.8±3.7	0.741Θ
Albumın (g/L) (reference range 32-48 g/L)	41.02±5.71	37.70±6.65	**0.003**Θ
PT (sn) (reference range 9.8-14 sn)	14.04±1,45	14.04±1.35	0.980Θ
APTT (sn) (reference range 21-32 sn)	25.71±2.61	26.28±3.38	0.297Θ
Fibrinogen (g/L) (reference range 1.7-4.2 g/L)	5.06±1.49	5.17±1.87	0.704Θ
D-Dimer (mg/L) (reference range <0.55 mg/L)	1.79 (0.37-12.2)	2.4 (0.26-35.2)	**0.009**#
Sedimentation rate (mm/h) (reference range 0-15 mm/h)	40 (3-117)	47 (3-132)	0.053#
C-reactive protein (mg/L) (reference range 0-5 mg/L)	130 (10-230)	150 (5-340)	**0.004**#
IL-6 (pg/mL) (reference range 0-0.34 pg/mL)	50.2 (2.62-3193)	65.9 (2-11328)	0.096#
Procalcitonin (ug/L) (reference range <0.16 ug/L)	1.24 (0.03-46.2)	1.7 (0.03-116)	0.060#
Ferritin (ug/L) (reference range 7-140 ug/L)	185 (65-2505)	250 (29-10690)	**0.002**#

#: Mann Whitney U test was used; Θ:Two independent sample t test was used; □: Pearson Chi Square test was used; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; Hb, haemoglobin; LVEF, left ventricle ejection fraction; LVFS, left ventricle fractional shortening; IL-6, interlökin-6; MAPSE, mitral annular plane systolic excursion; Na, sodium; TAPSE, tricuspid annular plane systolic excursion; Pro-BNP, N-terminal prohormone B-type natriuretic; PICU, paediatric intensive care unit; PT, prothrombin time; WBC; white blood cell.

found in the severity of cardiac involvement (p=0.25). Although not statistically significant in delta wave, Group 1 with the most severe cardiac involvement was the most frequently detected group. Fewer MIS-C patients were observed during the omicron wave. Groups 3 and 4, in which cardiac involvement was not at the forefront, were the most frequent groups (Fig. 2).

LV systolic dysfunction was normalized in most patients. Cardiac dysfunction was not detected in any patient at 3 months. In patients with CAAs in the acute period, all coronary artery z scores were normal after 1 month. The case fatality rate was 1.48%.

Discussion

Although many clinical features of KD and MIS-C are similar, diagnostic criteria help to differentiate the diseases. KD generally affects pediatric patients below the age of 5 years, whereas MIS-C affects children above the age of 5 years.[15] The median age of our patients diagnosed with MIS-C was 8.6 years. It was compatible with the literature. But, it remained unclear which patients would develop CAAs as in CD and which patients would develop myocardial dysfunction. We focused on the cardiac findings of the patients. Group 1 with decreased LVEF and CAAs was statistically older than Group 4 without cardiac involvement (median age 146 months, p: 0.008). The reason for this difference was thought to be decreased LVEF. To overcome this limitation, 15 patients in Group 1 (LVEF<55% and prominent CAAs) were older in median age (median age 158 months, p=0.003) compared to the patients in Group 3 (LVEF≥55%with prominent CAAs). The overall median age of patients with MIS-C was 104 months. Cardiac dysfunction in MIS-C patients seems to affect older children. Among the inflammatory markers, only elevated CRP was significant. Ludwikowska et al.[22] also found that CAAs developed more frequently in younger children, while they were significantly more frequent in older Children who have higher levels of inflammatory markers and contractility dysfunction at presentation. It supported the present study.

Table 2. Demographic, echocardiographic, laboratory and mortality results of patients with MIS-C according to groups

Variables (Median, Min-Max)	Group 1 n=29	Group 2 n=22	Group 3 n=29	Group 4 n=55	P	Pairwise comparisions					
						1vs2	1vs3	1vs4	2vs3	2vs4	3vs4
Age, months	146 (12-202)	132 (40-209)	81 (15-184)	98 (9-208)	0.008#	0.621	0.012	0.008	0.018	0.036	0.115
Male	16 (55.2%)	12 (54.5%)	17 (58.6%)	35 (63.6%)	0.089$^{\Theta}$	-	-	-	-	-	-
LVEF (%)	50.03±6.00	48.59±7.85	66.14±3.43	67.31±3.87	<0.001$^{\Theta}$	0.752	<0.001	<0.001	0.752	<0.001	0.752
LVFS (%)	24.72±4.21	23.86±5.20	35.59±2.75	36.45±3.22	<0.001$^{\Theta}$	0.848	<0.001	<0.001	<0.001	<0.001	0.743
MAPSE (mm)	10.90±3.35	10.47±2.44	11.40±2.11	12.22±1.91	0.061$^{\Theta}$	-	-	-	-	-	-
TAPSE (mm)	17.39±2.94	18.50±4.63	19.86±4.07	19.44±3.48	0.078$^{\Theta}$	-	-	-	-	-	-
Pro-BNP ng/L (reference range <125 ng/L)	6300 (35-35000)	5815 (180-35000)	1674 (17-35000)	1069 (54-19900)	<0.001#	0.834	0.013	<0.001	0.025	<0.001	0.110
Troponin ng/L (reference range <45 ng/L)	151 (2.5-7059)	255 (2.5-10810)	13 (2.5-1863)	7 (2-1511)	<0.001#	0.493	<0.001	<0.001	<0.001	<0.001	0.138
Length of stay in ward	5 (3-23)	8 (1-17)	8(0-20)	8 (3-19)	0.931#	-	-	-	-	-	-
Length of stay in PICU	5 (0-22)	5 (0-18)	0 (0-9)	0 (0-10)	<0.001#	0.962	0.003	<0.001	0.003	<0.001	0.177
Mortality	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)	0.331#	-	-	-	-	-	-
WBC (10^3/μL) (reference range 4.0–10.0 10^3/μL)	9670 (1100-37000)	10855 (1890-30000)	8700 (1100-21130)	7700 (2700-26100)	0.307#	-	-	-	-	-	-
Absolute neutrophil count (10^3/μL)	7705 (11-33600)	8725 (1640-27000)	6860 (790-16640)	5500 (1230-22700)	0.245#	-	-	-	-	-	-
Absolute lymphocyte count (10^3/μL)	950 (210-3400)	820 (310-2620)	1260 (210-3900)	1100 (300-5500)	0.461#	-	-	-	-	-	-
Hb (g/dL) (12.0–16.0)	11.62±1.16	12.19±2.84	11.67±1.69	12.37±1.47	0.179$^{\Theta}$	-	-	-	-	-	-
Platelets (10^3/μL) (reference range) 130–450 10^3/μL	212000 (48000-380000)	167500 (43000-340000)	221000 (48000-543000)	234000 (74000-550000)	0.172#	-	-	-	-	-	-
Na (mEq/L)reference range 132-146 mEq/L)	134.28±4.45	133.86±3.82	135.14±2.59	135.13±3.37	0.421$^{\Theta}$	-	-	-	-	-	-
AST (U/L) (reference range 0-40 g/L)	34 (16-141)	36 (10-96)	37 (13-135)	30 (11-328)	0.065#	-	-	-	-	-	-
ALT (U/L) (reference range 0-41 U/L)	27.0 (9-150)	28 (13-190)	27 (11-176)	19 (6-188)	0.016#	0.607	0.814	0.016	0.962	0.008	0.014
Albumın (g/L) (reference range 32-48 g/L)	37.28±6.20	37.45±7.07	38.00±6.88	41.18±5.67	0.015$^{\Theta}$	1.0	0.972	0.038	0.990	0.093	0.128
PT (sn) (reference range 9.8-14 sn)	14.08±1.31	14.31±1.71	13.94±1.37	13.96±1.33	0.767$^{\Theta}$	-	-	-	-	-	-
APTT (sn) (reference range 21-32 sn)	25.76±2.72	27.29±3.79	26.27±3.58	25.58±2.60	0.157$^{\Theta}$	-	-	-	-	-	-
Fibrinogen (g/L) (reference range 1.7-4.2 g/L)	5.12±1.84	5.51±2.12	4.92±1.70	5.08±1.50	0.683$^{\Theta}$	-	-	-	-	-	-
D-Dimer (mg/L) (reference range <0.55 mg/L)	2.50 (0.30-11.02)	3.85 (0.68-35.20)	2.50 (0.40-35.20)	1.89 (0.26-12.20)	0.059#	-	-	-	-	-	-
Sedimentation rate (mm/h) (reference range 0-15 mm/h)	48 (11-127)	53 (3-132)	45 (11-130)	42 (7-111)	0.511#	-	-	-	-	-	-
C-reactive protein (mg/L) (reference range 0-5 mg/L)	160 (5-340)	195 (10-320)	130 (10-220)	130 (10-230)	0.007#	0.131	0.043	0.007	0.017	0.005	0.756
Procalcitonin (ug/L) (reference range <0.16 ug/L)	4.0 (0.030-116.0)	4.1 (0.030-100.6)	1.3 (0.060-46.2)	1.3 (0.030-21.0)	0.076#	-	-	-	-	-	-
IL-6 (pg/mL) (reference range 0-0.34 pg/mL)	133 (2.0-1501)	114.5 (3.68-585.0)	50.2 (2.62-11328)	48.2 (4.20-982.7)	0.164#	-	-	-	-	-	-
Ferritin (ug/L) (reference range 7-140 ug/L)	403 (48-1614)	400 (103-10690)	250 (56.0-2505)	208 (29.0-1606)	0.011#	0.621	0.482	0.011	0.177	0.008	0.186

#: Kruskal Wallis H test was used. Mann Whitney U Test was used to pairwise comparisons and an adjusted alpha value for Bonferroni correction was 0.008. □: Pearson Chi Square test was used. $^{\Theta}$:One Way ANOVA was used. Tukey HSD test was used to pairwise comparisons; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; Hb: haemoglobin; LVEF: left ventricle ejection fraction; LVFS: left ventricle fractional shortening; IL-6: interlökin-6; MAPSE: mitral annular plane systolic excursion; Na: sodium; TAPSE: tricuspid annular plane systolic excursion; Pro-BNP, N-terminal prohormone B-type natriuretic; PICU: paediatric intensive care unit; PT: prothrombin time; WBC: white blood cell.

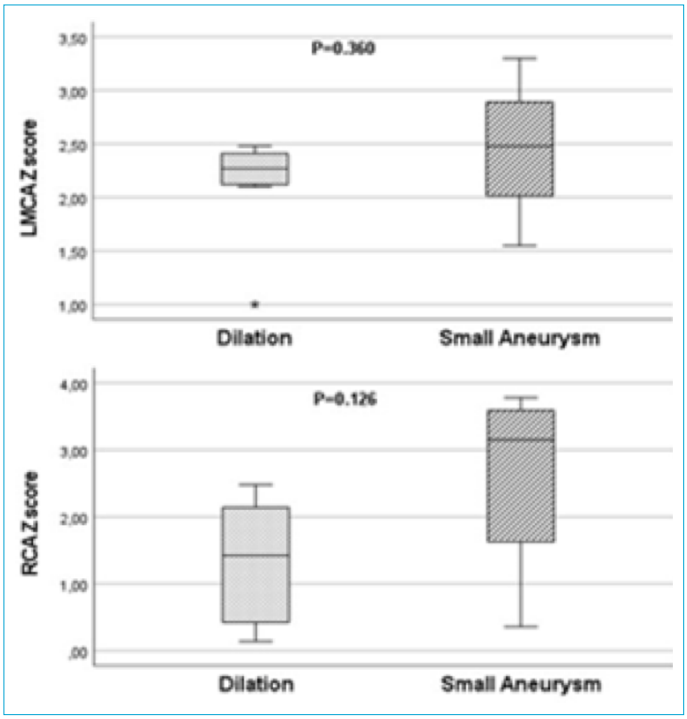

Figure 1. Coronary artery abnormalities detected in patients.

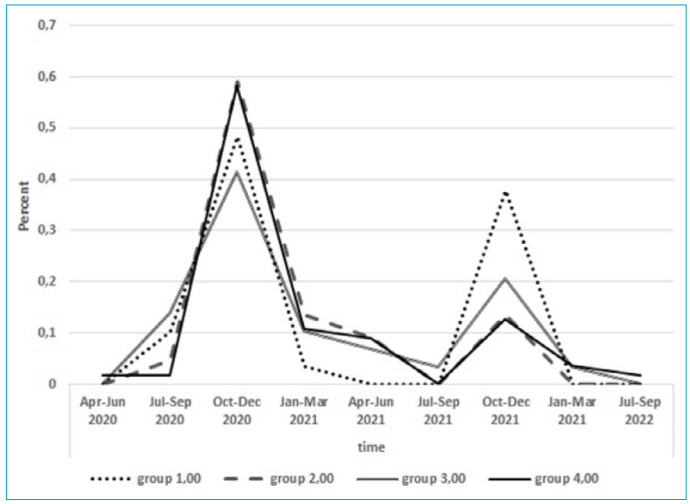

Figure 2. Percentage of groups according to date ranges.

Approximately 50% of patients develop LV systolic and/or diastolic dysfunction and 10-20% coronary artery dilatation and/or aneurysm.[23] It has been reported to be more frequent in male patients.[24] In the present study, 60.7% of the patients had cardiologic findings (mostly left ventricular dysfunction, myocarditis, coronary dilatation, and pericardial effusion). In the present study, the most frequent cardiac finding was left ventricular dysfunction, which is also reported in the literature, while coronary dilatation or aneurysm was seen less frequently.

Toubiana et al.[4] reported 18 patients whose echocardiography yielded coronary artery abnormalities in 8 (38%) MIS-C patients after a median of 7.5 (range 5-11) days of fever, which consisted of dilations (z score between 2.0 and 2.5) in five (24%) patients and increased echo-bright coronaries in 3 patients (14%). No coronary aneurysms were reported. In the present study, although the z score was normal in coronary arteries in 44 patients, prominent and/or increased echogenicity was noted in coronary arteries. We think that these findings may be secondary to inflammation in this newly defined disease, which has many questions to be explained. In the literature, despite normal measurements in patients with MIS-C, prominent coronary artery findings have been reported in the case series. Ramcharan et al.[9] in 7 of 15 patients, Kaushik et al.[25] in 6 of 33 patients, Cheung et al.[3] in 1 of 17 patients, and Chiotos et al.[26] in 1 of 6 patients reported prominent coronary arteries or echobright coronaries on echocardiogram but normal measurements. Perivascular brightness or echogenicity in the coronary arteries in CD has been removed from the diagnostic criteria over time.[18] We think that whether this finding in MIS-C will be accepted as CAAs in the future will be clarified with further studies.

The results regarding coronary artery dilatation and aneurysms in MIS-C have been favorable and many CAAs normalized within 30 days.[27,28] In the present study, we showed that coronary abnormalities regressed during the follow-up period. Arrhythmias and electrocardiographic changes have been reported in 28-67% of MIS-C patients.[29-31] The most frequent are low QRS amplitude and T-wave abnormalities.[27] A total of 6-25% patients had first-degree heart block more frequently than second or third-degree heart block, which is usually related to LV systolic dysfunction.[32] Arrhythmias and electrocardiographic changes were found in 37.7% of our patients. The most commonly observed abnormalities were T-wave changes, ST-segment elevation, and first-degree AV block.

During the COVID-19 pandemic, many new variants emerged and circulated as a result of mutations in the SARS-CoV-2 virus. These mutations could potentially increase the infectivity, pathogenicity, and antigenic capacity of the virus. The most important criteria for monitoring each new circulating variant as a public health problem were defined as an increase in the transmission rate, the potential to cause more severe clinical manifestations, and escape from immune response.[12-14] Little is known on how mutations affect the severity of cardiac involvement in MIS-C. In the study of Rojas et al.[33], patients diagnosed with MIS-C with a more severe clinical course in the second wave [20A to C, 20G, 21C (Epsilon), 20I (Alpha), and 20J (Gamma)] were followed up. We followed more patients diagnosed with MIS-C in the alpha wave of our country compared to other

waves, but no difference was found in terms of the severity of cardiac involvement. In the delta wave, we did not find any statistical significance, but Group 1, in which cardiac involvement was the highest, was the most frequently detected group. We think that the reason is related to the small sample size. A lower incidence of MIS-C was observed during the Omicron wave. Group 3 and Group 4, in which cardiac involvement was not at the forefront, were the most frequent groups.

Our study consists of MIS-C patients, but the sample size is limited. Additionally, as it is a retrospective study, the data were obtained solely from existing records, which may introduce potential errors and biases. Cardiac biopsy was not performed, and inflammatory/anti-inflammatory cytokines could not be analyzed. Therefore, further prospective studies and more comprehensive biomarker analyses are needed to gain a deeper understanding of the findings in our study.

In conclusion, cardiovascular involvement in MIS-C seems to affect age groups differently. Myocardial dysfunction affects older children. Patients followed up in the PICU were older children who have cardiac dysfunction. There was no difference in the severity of cardiac involvement according to the variants. Although cardiac involvement in MIS-C tends to improve, larger sample size randomized controlled trials are needed to evaluate long-term outcomes.

Disclosures

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References

1. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259–69. [Crossref]
2. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like dis-ease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771–8. [Crossref]
3. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. JAMA 2020;324:294–6. [Crossref]
4. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094. [Crossref]
5. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607–8. [Crossref]
6. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al; Overcoming COVID-19 investigators; CDC COVID-19 response team. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334–46.
7. Yilmaz Ciftdogan D, Ekemen Keles Y, Cetin BS, Dalgic Karabulut N, Emiroglu M, Bagci Z et al. COVID-19 associated multisystemic inflammatory syndrome in 614 children with and without overlap with Kawasaki disease-Turk MIS-C study group. Eur J Pediatr 2022;181:2031–43. [Crossref]
8. Palabiyik F, Akcay N, Sevketoglu E, Hatipoglu N, Sari EE, Inci E. Imaging of multisystem inflammatory disease in children (MIS-C) associated with COVID-19. Acad Radiol 2021;28:1200–8. [Crossref]
9. Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatr Cardiol 2020;41:1391–401. [Crossref]
10. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Pulmonol 2021;56:837–48. [Crossref]
11. Sirico D, Basso A, Reffo E, Cavaliere A, Castaldi B, Sabatino J, et al. Early echocardiographic and cardiac MRI findings in multisystem inflammatory syndrome in children. J Clin Med 2021;10:3360. [Crossref]
12. Harahsheh AS, Sharron MP, Bost JE, Ansusinha E, Wessel D, DeBiasi RL; Children's National Hospital MIS-C Taskforce. Comparison of first and second wave cohorts of multisystem inflammatory disease syndrome in children. Pediatr Infect Dis J 2022;41:e21–5. [Crossref]
13. Ptak K, Szymońska I, Olchawa-Czech A, Kukla K, Cisowska M, Kwinta P. Comparison of the course of multisystem inflammatory syndrome in children during different pandemic waves. Eur J Pediatr 2023;182:1647–56. [Crossref]
14. Belay ED, Abrams J, Oster ME, Giovanni J, Pierce T, Meng L, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr 2021;175:837–45. [Crossref]
15. You SD, Kim JH, You J. Clinical characteristics and short-term outcomes of multisystem inflammatory syndrome in a country with

a high prevalence of KD. Front Pediatr 2023;11:1088529. [Crossref]
16. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome (MIS). Available at: https://www.cdc.gov/mis/mis-c/hcp/index.html. Accessed Dec 5, 2023.
17. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr 2009;22:715–9. [Crossref]
18. Koestenberger M, Nagel B, Ravekes W, Avian A, Heinzl B, Fritsch P, et al. Left ventricular long-axis function: reference values of the mitral annular plane systolic excursion in 558 healthy children and calculation of z-score values. Am Heart J 2012;164:125–31. [Crossref]
19. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, et al; Northwell Health COVID-19 Research Consortium. Characteristics, cardiac involvement, and outcomes of multisystem inflammatory syndrome of childhood associated with severe acute respiratory syndrome coronavirus 2 infection. J Pediatr 2020;224:141–5. [Crossref]
20. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927–99. Erratum in: Circulation 2019;140:e181–4. [Crossref]
21. World Health Organization. Tracking SARS-CoV-2 variants. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed Apr 19, 2024.
22. Ludwikowska KM, Moksud N, Tracewski P, Sokolski M, Szenborn L. Cardiac involvement in patients with multisystem inflammatory syndrome in children (MIS-C) in Poland. Biomedicines 2023;11:1251. [Crossref]
23. Yasuhara J, Masuda K, Watanabe K, Shirasu T, Takagi H, Sumitomo N, et al. Longitudinal cardiac outcomes of multisystem inflammatory syndrome in children: a systematic review and meta-analysis. Pediatr Cardiol 2023;44:892–907. [Crossref]
24. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health 2021;5:323–31. [Crossref]
25. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem inflammatory syndrome in children asso ciated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr 2020;224:24–9. [Crossref]
26. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. J Pediatric Infect Dis Soc 2020;9:393–8. [Crossref]
27. Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol 2020;76:1947–61. [Crossref]
28. Shaykh R, Leftin S, Suh S, Spencer R, Gorelik M, Wilson PT, Diamond R. Reversible coronary artery aneurysm with delayed anti-inflammatory therapy in multisystem inflammatory syndrome in children. JACC Case Rep 2021;3:550–4. [Crossref]
29. Dionne A, Newburger JW. The electrocardiogram in multisystem inflammatory syndrome in children: mind your Ps and Qs. J Pediatr. 2021;234:10–11. [Crossref]
30. Regan W, O'Byrne L, Stewart K, Miller O, Pushparajah K, Theocharis P, Wong J, Rosenthal E. Electrocardiographic changes in children with multisystem inflammation associated with COVID-19: associated with Coronavirus disease 2019. J Pediatr. 2021;234:27–32.e22. [Crossref]
31. Haghighi Aski B, Manafi Anari A, Abolhasan Choobdar F, Zareh Mahmoudabadi R, Sakhaei M. Cardiac abnormalities due to multisystem inflammatory syndrome temporally associated with Covid-19 among children: a systematic review and meta-analysis. Int J Cardiol Heart Vasc. 2021;33:100764. [Crossref]
32. Hallberg TC, Bjorklund AR, Slusher TM, Rodgers N. Sinus bradycardia in a toddler with multisystem inflammatory syndrome in children (MIS-C) related to COVID-19. BMJ Case Rep 2021;14(5):e242058. [Crossref]
33. Moreno Rojas AF, Bainto E, Harvey H, Tremoulet AH, Burns JC, Dummer KB. SARS-CoV-2 variants are associated with different clinical courses in children with MIS-C. World J Pediatr 2024;20:143–52. [Crossref]