Cardiology in the Young

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Cardiac effects of COVID-19 infection in children

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Original Article

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Abstract

Background: It is known established that the cardiac effects of COVID-19 infection are associated with poor prognosis and high mortality rates in infected patients. The aim of this study was to evaluate the cardiac effects of COVID-19 infection in paediatric patients and identify the correlations between clinical and laboratory data and the degree of cardiac involvement. *Materials and Methods:* A retrospective data analysis was conducted on 64 paediatric patients at Gazi University Department of Pediatrics who were treated as inpatients with a diagnosis of COVID-19. Patients were classified as "COVID-19-related cardiac involvement cases" if their electrocardiogram and echocardiogram results indicated a pathology and/or if their laboratory data indicated increased cardiac enzymes. All patients were divided into subgroups based on whether they had cardiac involvement and whether they were diagnosed with multisystem inflammatory syndrome in children. *Results:* In comparison to patients who did not have cardiac involvement, those with cardiac involvement had significantly higher levels of hs-Troponin T, Pro-BNP, and D-dimer. Patients with multisystem inflammatory syndrome in children had significantly longer PR intervals than those without multisystem inflammatory syndrome in children ($p = 0.0001$). Patients with multisystem inflammatory syndrome in children had a significantly higher rate of pathological valve insufficiencies (68.1%) than those without multisystem inflammatory syndrome in children (14.2%) ($p = 0.001$). *Conclusion:* In our study, the strongest predictive biomarker of cardiac involvement in paediatric patients with COVID-19 infection was determined to be hs-Troponin T. It was observed that pathologic electrocardiogram changes could reflect cardiac involvement in the absence of any other signs. Patients with multisystem inflammatory syndrome in children exhibited significantly greater rates of pathologic echocardiogram findings and myocardial dysfunction than those without multisystem inflammatory syndrome in children. In all patients, pathologic electrocardiogram and echocardiogram findings were found to be strongly associated with the severity of inflammation.

Since the identification of the novel COVID-19, which led to the onset of a pandemic, in December 2019, researchers and practitioners have been working to understand both the acute and long-term effects of the disease.[1] In addition to its effects that are seen predominantly in the respiratory tract, COVID-19 infection can also result in cardiological, haematological, and neurological complications, as well as secondary bacterial infections.[2] Respiratory failure is the most frequently encountered cause of mortality in COVID-19 patients. Cardiac complications, identified as the second most common cause,[3] are extensively supported by evidence to indicate that those observed in COVID-19—including acute myocardial dysfunction, arrhythmias, coronary artery dilatation and aneurysms, and left ventricular systolic dysfunction—are triggered by systemic hyperinflammation resulting from viral infection.[4] It is known that cardiac complications in COVID-19 are associated with poor prognosis and high mortality rates.[5] For this reason, the early identification of cardiac effects can change the management of the disease, as well as its prognosis. However, there is limited information in the literature about cardiac effects associated with COVID-19 in children.

In our study, we analysed biochemical parameters, along with echocardiographic and electrocardiographic findings, to assess how the severity of inflammation and clinical manifestations impact the cardiovascular system in paediatric patients with COVID-19. These parameters were categorised into four subgroups based on whether the patients were diagnosed with multisystem inflammatory syndrome in children and whether they exhibited cardiac involvement. We believe that our study will enhance the existing literature by examining distinctions among these groups.

Material and methods

Study population and design

This was a single-centre, retrospective, and non-invasive clinical study that was carried out with the data of patients who were diagnosed with COVID-19. Information was collected on the complaints of the included patients at the time of their presentation, their physical examination findings, and their laboratory parameters at the time of their diagnosis (complete blood count, biochemical parameters, and inflammatory markers). Additionally, the findings of all electrocardiogram and echocardiogram examinations of the patients throughout their hospital admission were searched, and their data were recorded.

The study included paediatric patients aged 0–18 who were monitored with the diagnosis of COVID-19 as inpatients in the Department of Pediatrics at Gazi University Faculty of Medicine between March 2020 and March 2022. The reasons for the admission of the patients to the hospital were a severe clinical course of COVID-19 infection, a poor general state of health, the development of disease-related complications, and/or secondary bacterial infections.

Due to COVID-19 not showing specific differences in clinical symptoms from other viral infections, the definitive diagnosis is established through microbiological tests. According to the protocols and recommendations of the World Health Organization, the reverse transcription polymerase chain reaction test is utilised for the identification and confirmation of COVID-19 patients.[6] The gold standard method for diagnosis involves detecting the viral genome using the reverse transcription polymerase chain reaction method on samples taken from the respiratory tract of the infected individual (such as swabs from the oropharynx and nasopharynx, sputum, and bronchoalveolar lavage).[7] Especially in individuals exhibiting symptoms of COVID-19, the reverse transcription polymerase chain reaction method is employed to confirm the disease and screen those who have been in contact with a COVID-19 patient. An alternative method of diagnosis involves serological tests, specifically immunoglobulin M and G, which reveal the presence of specific antibodies developed against the agent in the patient's serum.[8] These tests identify antibodies formed in response to SARS-CoV-2 in the bloodstream. In our study, we included patients with confirmed COVID-19 diagnoses based on either polymerase chain reaction positivity or antibody positivity. Patients with congenital or acquired cardiac disease, patients with arrhythmia, patients with systemic diseases that may affect biochemical parameters, people who were not diagnosed with COVID-19, and people under outpatient follow-up were excluded from the study.

Patients who showed a pathology in their electrocardiogram and echocardiogram results and/or cardiac enzyme elevation in their laboratory findings were defined as "COVID-19-related cardiac involvement" cases. Based on this definition, all patients were divided into two groups as those with cardiac involvement (Group 1) and those without cardiac involvement (Group 2). All patients were also divided into subgroups of those with and without the diagnosis of multisystem inflammatory syndrome in children. While identifying the multisystem inflammatory syndrome in children statuses of the patients, the Management and Treatment Guidebook for Pediatric COVID-19 Patients of the Turkish Ministry of Health was utilised. Intragroup and intergroup comparisons were made in all groups and subgroups for all examined parameters.

Evaluation of biochemical parameters

Haemoglobin, haematocrit, red blood cell count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width, platelet count, mean platelet volume, white blood cell count, absolute neutrophil count, neutrophil percentage, absolute lymphocyte count and lymphocyte percentage, monocyte percentage, eosinophil percentage, and basophil percentage were recorded as parameters of complete blood count. From the patients' biochemical parameters, values for creatine kinase, creatine kinase MB, high-sensitivity cardiac troponin T, and pro-brain natriuretic peptide were recorded. Inflammatory markers include C-reactive protein, erythrocyte sedimentation rate, procalcitonin, D-dimer, ferritin, and fibrinogen data.

Electrocardiographic evaluation

Measurements of PR interval, QRS interval and corrected qt interval were evaluated based on 12-lead spot electrocardiograms taken during patients' hospitalisations. The QTc calculation was performed using the Bazett formula. Additionally, rhythm and axis information was recorded. Any ST segment and T wave changes, atrial dilation, and signs of ventricular hypertrophy were documented if present. If multiple electrocardiograms were taken during the patients' hospitalisations, the electrocardiogram with identified pathological findings was taken into consideration.

Echocardiographic evaluation

The measurements were made by the same practitioner using a GE Vivid 3 device (GE Ultrasound, Horten, Norway) with 3.5 and 5 MHz probes to include both inspiration and expiration. Echocardiography was assessed using images obtained through standard parasternal long-axis, parasternal short-axis, apical four-chamber, subcostal, and suprasternal sections. Systolic and diastolic functions, valve functions, pericardial effusion, and vegetation findings were evaluated and recorded. Systolic functions of the left ventricle were obtained using M-mode on the parasternal long-axis section. Values below 55% for ejection fraction were defined as impaired systolic function. Diastolic functions were evaluated using pulse wave Doppler on the mitral and tricuspid valves, assessing early and late diastolic flows. In the study, diastolic functions were categorised as normal or impaired. Previously nonexistent aortic insufficiencies were considered significant in patients. However, in children, physiological tricuspid, pulmonary, and mitral valve insufficiencies are common, so insufficiencies deemed pathological in these valves were considered significant. Doppler flow velocity above 3 m/s, pansystolic insufficiencies for the mitral valve, and insufficiencies of grade 1 and above for the tricuspid and pulmonary valves were considered significant. If there are multiple echocardiogram assessments during a patient's hospitalisation, echocardiogram data with pathological findings were taken into account.

Statistical analysis

The SPSS 24.0 (SPSS, Chicago, IL, US) programme was used to analyse the collected data and create tables. Chi-squared tests were used to compare the groups based on the categorical variables. Depending on whether the data were normally distributed or not, student's t-test or the Mann-Whitney U test was utilised to compare the numeric variables between two groups. Depending on the normality of the distribution of the data, Spearman's or

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Pearson's correlation analyses were conducted to identify relationships between numeric variables. The diagnostic value of D-dimer levels for cardiac involvement was calculated by the receiver operating characteristic analysis method. Sensitivity and specificity values were also analysed in the patients with cardiac involvement based on the D-dimer threshold value. Univariate chi-squared tests were carried out, and odds ratio and 95% confidence interval values were calculated. The level of statistical significance was accepted as $p < 0.05$.

Written informed consent was signed by the parents of all children. This study was conducted in compliance with the "Declaration of Helsinki" and was approved by the Gazi University Clinical Research Ethics Committee (decision no: 342, date: 16.05.2022).

Results

The data of a total of 64 patients who met the inclusion criteria were analysed. While 53.1% (n = 34) of the patients were female, 46.9% (n = 30) were male, and the mean age of all patients was 8 ± 4.7 years.

Group 1, designated as the group of patients with COVID-19-related cardiac involvement, included 34 patients, while Group 2, designated as the group of patients without COVID-19-related cardiac involvement, included 30 patients. There were 22 patients diagnosed with multisystem inflammatory syndrome in children and 42 patients without the diagnosis of multisystem inflammatory syndrome in children. The COVID-19 PCR tests of 31.3% (n = 20) of the patients were positive, while the COVID-19 immunoglobulin G antibody tests of the remaining 68.7% (n = 44) were positive despite having negative COVID-19 polymerase chain reaction test results.

The symptoms of the patients at the time when they presented to the hospital were fever (85.9%, n = 55), diarrhoea (29.7%, n = 19), rashes (26.6%, n = 17), malaise (23.4%, n = 15), cough (18.8%, n = 12), respiratory distress (15.6%, n = 10), headache (14.1%, n = 9), and chest pain (7.8%, n = 5). The most prevalent symptom at presentation was fever.

Comparison of patients with and without cardiac involvement

In Group 1, among the 34 patients with cardiac involvement, 16 (47.1%) were female and 18 (52.9%) were male. In Group 2, among the 30 patients without cardiac involvement, 18 (60%) were female and 12 (40%) were male. The mean age of the patients in Group 1 was 7.8 years, whereas the mean age of the patients in Group 2 was 8.3 years. Cardiac involvement was identified in 34 (53.1%) of all 64 patients. Only the complaint of malaise was significantly more frequent in Group 1 ($p = 0.0001$) (Table 1).

There was no statistically significant difference between the two groups in terms of their complete blood count test results ($p > 0.05$). In comparison to the patients in Group 2, the patients in Group 1 had significantly higher CK, hs-Troponin T, Pro-BNP, and D-dimer values (Table 2). As a result of the receiver operating characteristic analysis of Pro-BNP in the patients for cardiac involvement, the "cut-off" value was determined to be 205 pg/mL. It was observed that Pro-BNP values higher than this value indicated cardiac involvement with 67% sensitivity and 67% specificity. As a result of the receiver operating characteristic analysis of D-dimer in the patients for cardiac involvement, the "cut-off" value was determined to be 1.49 µg/mL. It was observed that D-dimer values higher than this value indicated cardiac involvement with 70% sensitivity and 69%.

Table 1. Comparison of presenting symptoms between Group 1 (with cardiac involvement) and Group 2 (without cardiac involvement)

	Group 1 (n = 34)	Group 2 (n = 30)	p
Fever			0.30
Yes, *n* (%)	28 (82.3%)	27 (90%)	
No, *n* (%)	6 (17.7%)	3 (10%)	
Malaise			**0.0001**
Yes, *n* (%)	14 (41.1%)	1 (3.3%)	
No, *n* (%)	20 (58.9%)	29 (96.9%)	
Rashes			0.58
Yes, *n* (%)	10 (29.4%)	7 (23.3%)	
No, *n* (%)	24 (70.6%)	23 (76.7%)	
Diarrhoea			0.54
Yes, *n* (%)	9 (26.5%)	10 (33.3%)	
No, *n* (%)	25 (73.5%)	20 (66.7%)	
Cough			0.68
Yes, *n* (%)	7 (20.5%)	5 (16.7%)	
No, *n* (%)	27 (79.5%)	25 (83.3%)	
Chest Pain			0.21
Yes, *n* (%)	4 (11.8%)	1 (3.3%)	
No, *n* (%)	30 (88.2%)	29 (96.7%)	
Headache			0.30
Yes, *n* (%)	6 (17.6%)	3 (10%)	
No, *n* (%)	28 (82.4%)	27 (90%)	
Respiratory Distress			0.20
Yes, *n* (%)	7 (20.5%)	3 (10%)	
No, *n* (%)	27 (79.5%)	27 (90%)	

In the comparisons of the electrocardiogram and echocardiogram findings of the patients in Groups 1 and 2, PR intervals, QTc intervals, and pathologic valve insufficiencies detected in echocardiogram were significantly higher in Group 1 than in Group 2 ($p = 0.0001$). Moreover, the QTc intervals of three patients in Group 1 (8.8%) were longer than normal based on their ages (Table 3).

Comparison of patients with and without multisystem inflammatory syndrome in children diagnosis

Multisystem inflammatory syndrome in children was diagnosed in 22 (34.3%) of all 64 patients. Among the 22 patients with the diagnosis of multisystem inflammatory syndrome in children, 10 (45.5%) were female and 12 (54.5%) were male. Furthermore, among the 42 patients without the diagnosis of multisystem inflammatory syndrome in children, 24 (57.2%) were female and 18 (42.8%) were male. There was no significant difference between the two subgroups in terms of the demographic data of the patients ($p > 0.05$). It was found that 18 (81.8%) of the 22 patients diagnosed with multisystem inflammatory syndrome in children also had cardiac involvement. It was determined that 16 (38%) of the 42 patients who were not diagnosed with multisystem

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Table 2. Comparison of laboratory parameters between Group 1 (with cardiac involvement) and Group 2 (without cardiac involvement)

	Group 1 (n = 34)	Group 2 (n = 30)	p
Hb (gr/dl)	11.23 ± 0.33	11.06 ± 0.34	0.72
Hct (%)	34.39 ± 1.01	33.9 ± 1	0.73
RBC (10^6/μL)	4.16 ± 0.11	4.08 ± 0.14	0.65
MCV (fL)	82.26 ± 1.19	83.64 ± 1.86	0.52
MCH (pg)	27.05 ± 0.46	26.96 ± 0.75	0.90
MCHC (gr/dL)	32.83 ± 0.28	32.6 ± 0.17	0.47
RDW (%)	15.2 ± 0.7	15.12 ± 0.39	0.91
PLT (10^3/μL)	273,117 ± 33,466	291,500 ± 28,606	0.68
MPV (fL)	8.26 ± 0.33	8.61 ± 0.3	0.44
WBC (10^3/μL)	10,907 ± 1,270	10,136 ± 1,037	0.64
ANS (10^3/μL)	7,809 ± 1,110	6,597 ± 719	0.36
Neutrophil (%)	65.26 ± 21.91	64.98 ± 15.07	0.67
ALS (10^3/μL)	2,106 ± 300	2,358 ± 354	0.58
Lymphocyte (%)	22.41 ± 2.23	23.52 ± 2.27	0.72
Monocyte (%)	9.07 ± 1.55	10.97 ± 1.15	0.34
Eosinophil (%)	1.96 ± 0.67	1.23 ± 0.3	0.35
Basophil (%)	0.68 ± 0.29	0.37 ± 0.03	0.32
CK (U/L)	158.9 ± 52.81	37.05 ± 6.45	**0.03**
CK-MB (ng/mL)	14.09 ± 4.57	13.8 ± 5.98	0.97
hs-Troponin T (ng/L)	132.4 ± 48.6	12.8 ± 3.9	**0.023**
Pro-BNP (pg/mL)	3,865 ± 1,474	442.03 ± 245.94	**0.03**
CRP (mg/L)	102.95 ± 18.04	105.77 ± 15.79	0.90
ESR (mm/St)	60.96 ± 5.68	69.6 ± 6.9	0.33
PCT (ng/mL)	9.1 ± 4.9	0.99 ± 0.47	0.11
Ferritin (ng/mL)	468.4 ± 149.1	1,418 ± 897.5	0.30
Fibrinogen (mg/dL)	461.3 ± 28.1	483.5 ± 32.2	0.60
D-dimer (μg/mL)	4.65 ± 1.17	1.95 ± 0.46	**0.039**

CK = creatine kinase; CK-MB = creatine kinase MB; hs-Troponin T = high-sensitivity cardiac troponin T; Pro-BNP = pro-brain natriuretic peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PCT = procalcitonin.

inflammatory syndrome in children had cardiac involvement. The frequencies of rashes and headaches in the patients who had multisystem inflammatory syndrome in children were significantly greater than those in the patients who did not have multisystem inflammatory syndrome in children (rashes: $p = 0.002$, headaches: $p = 0.037$) (Table 4).

As expected, compared to the patients without multisystem inflammatory syndrome in children, the patients with multisystem inflammatory syndrome in children had significantly higher neutrophil counts and percentages and significantly lower lymphocyte and monocyte percentages. The patients with multisystem inflammatory syndrome in children also had significantly higher mean CK and CK-MB values than those without multisystem inflammatory syndrome in children ($p < 0.05$). Similarly, hs-Troponin T levels, Pro-BNP levels, and D-dimer levels were significantly higher among the patients with multisystem inflammatory syndrome in children in comparison to those without multisystem inflammatory syndrome in children (respectively, $p = 0.028$, $p = 0.019$, and $p = 0.036$). There was no statistically significant difference between the patients with multisystem inflammatory syndrome in children and those without multisystem inflammatory syndrome in children in terms of their inflammatory markers including CRP, PCT, ferritin, and fibrinogen values (Table 5).

The electrocardiogram data of the patients with and those without multisystem inflammatory syndrome in children diagnosis were compared in terms of both electrocardiogram intervals and pathologic electrocardiogram findings. The patients with and without multisystem inflammatory syndrome in children, respectively, had mean PR intervals of 0.17 s and 0.13 s ($p = 0.0001$), QTc intervals of 0.40 s and 0.39 s ($p = 0.08$), and QRS intervals of 0.07 s and 0.07 s ($p = 0.73$). In the subgroup of patients diagnosed with multisystem inflammatory syndrome in children, three (13.6%) patients had prolonged PR intervals, two (9%) had prolonged QTc intervals, one (4.5%) had pathologic ST-T variations, one (4.5%) had signs of ventricular hypertrophy, and two (9%) had signs of arrhythmia. In the subgroup of patients not diagnosed with multisystem inflammatory syndrome in children, one (2.4%)

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Table 3. Comparison of electrocardiogram and echocardiogram findings between Group 1 (with cardiac involvement) and Group 2 (without cardiac involvement)

	Group 1 (n = 34)	Group 2 (n = 30)	p
Mean PR interval, (s)	0.16 ± 0.03	0.13 ± 0.02	**0.0001**
Prolonged PR, *n* (%)	4 (11.7%)	0 (0%)	0.11
Mean QTc interval, (s)	0.41 ± 0.03	0.39 ± 0.02	**0.0001**
Prolonged QTc, *n* (%)	3 (8.8%)	0 (0%)	0.24
Mean QRS interval, (s)	0.07 ± 0.001	0.07 ± 0.01	0.47
ST-T variation, *n* (%)	3 (8.8%)	0 (0%)	0.24
Ventricular hypertrophy signs, *n* (%)	2 (5.9%)	0 (0%)	0.49
Arrhythmia signs, *n* (%)	2 (5.9%)	0 (0%)	0.49
Ejection fraction (%)	66.8 ± 1.52	71.03 ± 1.23	0.10
Systolic dysfunction, *n* (%)	2 (5.9%)	0 (0%)	0.49
Normal systolic func., *n* (%)	32 (94.1%)	30 (100%)	0.49
Diastolic dysfunction, *n* (%)	2 (5.9%)	0 (0%)	0.49
Normal Diastolic func., *n* (%)	32 (94.1%)	30 (100%)	0.49
Valve insufficiencies, *n* (%)	21 (61.8%)	0 (0%)	**0.0001**
Pericardial effusion, *n* (%)	5 (14.7%)	0 (0%)	0.055
Cardiac vegetation, *n* (%)	1 (2.9%)	0 (0%)	0.53
Coronary aneurism, *n* (%)	3 (8.8%)	0 (0%)	0.24

QTc = corrected qt interval.

patient had a prolonged PR interval, one (2.4%) had a prolonged QTc interval, two (4.8%) had pathologic ST-T variations, and one (2.4%) had signs of ventricular hypertrophy. In the comparisons of the echocardiogram findings of the two subgroups, the mean ejection fraction value of the subgroup of patients with multisystem inflammatory syndrome in children was found to be significantly lower ($p < 0.05$). The rate of pathologic valve insufficiencies was also significantly higher in the subgroup of patients with multisystem inflammatory syndrome in children compared to the subgroup of patients without multisystem inflammatory syndrome in children ($p = 0.001$) (Table 6).

COVID-19-related cardiac involvement was observed in 18 (81.8%) of the 22 patients with multisystem inflammatory syndrome in children, while the remaining four (18.2%) patients did not have COVID-19-related cardiac involvement. Among the 42 patients without a multisystem inflammatory syndrome in children diagnosis, 16 (38.1%) had cardiac involvement, while the remaining 26 (61.9%) did not. The laboratory values, electrocardiogram findings, and echocardiogram findings of the four subgroups were compared. The subgroup with both multisystem inflammatory syndrome in children and cardiac involvement had significantly higher hs-Troponin T and Pro-BNP values compared to the subgroup without multisystem inflammatory syndrome in children and with cardiac involvement (respectively, $p = 0.02$ and $p = 0.01$ for hs-Troponin T and Pro-BNP). There was no statistically significant difference between the subgroups of patients with and without cardiac involvement who were not diagnosed with multisystem inflammatory syndrome in children in terms of the compared parameters. The subgroup of patients with both multisystem inflammatory syndrome in children and cardiac involvement had significantly greater CK values ($p = 0.034$) compared to the subgroup with neither multisystem inflammatory syndrome in children nor cardiac involvement (Table 7).

PR intervals were significantly longer in the subgroup with multisystem inflammatory syndrome in children and with cardiac involvement compared to the subgroup without multisystem inflammatory syndrome in children and with cardiac involvement ($p = 0.002$). QTc intervals were significantly longer in the subgroup without multisystem inflammatory syndrome in children and with cardiac involvement compared to the subgroup without multisystem inflammatory syndrome in children and without cardiac involvement ($p = 0.008$) (Table 8). EF measurements were significantly lower in the subgroup with multisystem inflammatory syndrome in children and with cardiac involvement compared to the subgroup without multisystem inflammatory syndrome in children and with cardiac involvement ($p = 0.001$). The rate of pathologic valve insufficiencies in the subgroup without multisystem inflammatory syndrome in children and with cardiac involvement was significantly greater than the rate in the subgroup without multisystem inflammatory syndrome in children and without cardiac involvement ($p = 0.002$) (Table 8).

Discussion

Cardiac complications, such as acute myocardial dysfunction, arrhythmias, coronary artery dilatation, aneurysms, valve insufficiencies, and left ventricular systolic dysfunction, are observed in both COVID-19 and multisystem inflammatory syndrome in children, constituting some of the most life-threatening and significant morbidities. In our study, we classified our patient groups into four subgroups based on the diagnosis of multisystem inflammatory syndrome in children and the presence of cardiac involvement. Biochemical parameters, as well as echocardiographic and electrocardiographic findings, were organised into these four subgroups. The study results revealed that elevated levels of hs-Troponin T were a primary indicator of cardiac involvement. In addition, proBNP elevation is closely associated with cardiac

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Table 4. Comparison of presenting symptoms between the patients with and without multisystem inflammatory syndrome in children (MIS-C) diagnosis

	MIS-C + (n = 22)	MIS-C - (n = 42)	p
Fever			0.33
Yes, *n* (%)	20 (91%)	35 (83.3%)	
No, *n* (%)	2 (9%)	7 (16.7%)	
Malaise			0.25
Yes, *n* (%)	7 (31.8%)	8 (19%)	
No, *n* (%)	15 (68.2%)	34 (81%)	
Rashes			**0.002**
Yes, *n* (%)	11 (50%)	6 (14.3%)	
No, *n* (%)	11 (50%)	36 (85.7%)	
Diarrhoea			0.15
Yes, *n* (%)	9 (40.9%)	10 (23.8%)	
No, *n* (%)	13 (59.1%)	32 (76.2%)	
Cough			0.13
Yes, *n* (%)	2 (9%)	10 (23.8%)	
No, *n* (%)	20 (91%)	32 (76.2%)	
Chest Pain			0.21
Yes, *n* (%)	3 (13.6%)	2 (4.8%)	
No, *n* (%)	19 (86.4%)	40 (95.2%)	
Headache			**0.037**
Yes, *n* (%)	6 (27.2%)	3 (7.1%)	
No, *n* (%)	16 (72.8%)	39 (92.9%)	
Respiratory Distress			0.074
Yes, *n* (%)	1 (4.5%)	9 (21.4%)	
No, *n* (%)	21 (95.5%)	33 (78.6%)	

involvement. In our research, alterations in the electrocardiogram, particularly elevated D-dimer values, served as crucial indicators of cardiac involvement.

The myocardial damage observed in COVID-19 infections, characterised by severe inflammation, results in an increase in biomarkers such as CK-MB, hs-Troponin T, and Pro-BNP.[9–13] In our investigation, akin to this, CK, hs-Troponin T, and Pro-BNP levels exhibited a notable increase in patients with cardiac involvement compared to those without such involvement. When comparing patients with and without multisystem inflammatory syndrome in children, significant elevations in CK, CK-MB, hs-Troponin T, and Pro-BNP values were observed in those diagnosed with multisystem inflammatory syndrome in children. However, only hs-Troponin T levels exhibited significant variation between patients with both multisystem inflammatory syndrome in children and cardiac involvement and those with cardiac involvement alone, with higher values in the former group than in the latter. This difference may be explained by the possibility that between these two subgroups with cardiac involvement, the cardiac injury in the group with multisystem inflammatory syndrome in children was more severe. This may also suggest that while the CK, CK-MB, and Pro-BNP values of different subgroups also indicated the presence or absence of cardiac involvement, the most sensitive marker was hs-Troponin T. This is because, although total CK values were determined to be different between the patients with cardiac involvement and those without cardiac involvement, there was no significant difference between the CK-MB values of these groups. Again, among the patients with cardiac involvement in our study, those who also had multisystem inflammatory syndrome in children showed significantly higher hs-Troponin T and Pro-BNP values compared to those without multisystem inflammatory syndrome in children. This result also implies that the cardiac damage in patients with multisystem inflammatory syndrome in children in addition to cardiac involvement is more severe than that in patients with isolated cardiac involvement.

Elevated levels of inflammatory parameters such as D-dimer, CRP, ESR, PCT, fibrinogen, and ferritin have been shown as a consequence of the severe inflammation observed in COVID-19 cases.[10,14–16] In our study, patients, who were symptomatic with a severe clinical course, generally exhibited heightened levels of inflammatory markers. However, when examining the connections between inflammatory markers and cardiac involvement, our study revealed that cardiac issues were specifically linked to a noteworthy increase in D-dimer levels, while no significant associations were found with CRP, ESR, PCT, fibrinogen, or ferritin levels. D-dimer levels were also significantly higher in the subgroups with the diagnosis of multisystem inflammatory syndrome in children compared to those without the diagnosis of multisystem inflammatory syndrome in children. Nonetheless, it should be kept in mind that D-dimer levels are not a parameter that is directly related to cardiac functions. Considering that most of the patients diagnosed with multisystem inflammatory syndrome in children in our study had cardiac involvement, it would be more accurate to think that elevated D-dimer levels were associated with the severity of inflammation, rather than the presence of cardiac involvement. The absence of a significant difference between the D-dimer levels of the patients with and without cardiac involvement in the subgroups with multisystem inflammatory syndrome in children supported this view. D-dimer, originating from fibrin breakdown in thrombus, is elevated as a marker in vascular thromboembolic events. Additionally, it rises in states of inflammation as an acute phase reactant and possesses a high negative predictive value.[17] COVID-19 patients commonly exhibit a predisposition to coagulation disorders. Studies have shown that markedly elevated D-dimer levels in patients hospitalised in ICUs may be associated with the mortality of the disease.[18] In a study conducted in 2022 with COVID-19 polymerase chain reaction-positive patients, it was demonstrated that D-dimer levels were significantly higher in children who were both polymerase chain reaction-positive and had pneumonia compared to those who were only polymerase chain reaction-positive and did not have pneumonia.[19] In a study involving 14 children with a positive Omicron variant of COVID-19, it was noted that 78% of the patients exhibited elevated D-dimer levels.[20] Many studies in the literature have shown correlations between the severity of COVID-19 infections and inflammatory markers including D-dimer, even though they have varying different values and ratios.[21–24]

Our findings indicated a strong correlation between electrocardiogram changes and cardiac involvement, suggesting that these changes could serve as the sole indicator of cardiac issues in certain patients. In the group of patients with cardiac involvement in this study, the mean PR and QTc intervals were significantly prolonged compared to those in the group without cardiac involvement. Two patients with supraventricular tachycardia had

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Table 5. Comparison of laboratory parameters between the patients with and without multisystem inflammatory syndrome in children (MIS-C) diagnosis

	MIS-C + (n = 22)	MIS-C - (*n* = 42)	p
Hb (gr/dl)	10.91 ± 0.36	11.2 ± 0.31	0.46
Hct (%)	33.4 ± 1.08	34.5 ± 0.92	0.46
RBC (10^6/μL)	4.13 ± 0.12	4.12 ± 0.12	0.93
MCV (fL)	80.54 ± 1.35	84.15 ± 1.44	0.11
MCH (pg)	26.51 ± 0.59	27.27 ± 0.57	0.40
MCHC (gr/dL)	32.88 ± 0.37	32.64 ± 0.16	0.51
RDW (%)	15.7 ± 1.05	14.8 ± 0.3	0.27
PLT (10^3/μL)	250,954 ± 40,314	297,857 ± 26,302	0.31
MPV (fL)	8.07 ± 0.50	8.61 ± 0.22	0.27
WBC (10^3/μL)	12,389 ± 1,603	9,580 ± 918.7	0.10
ANS (10^3/μL)	9,442 ± 1,373	6,088 ± 602.02	**0.037**
Neutrophil (%)	72.6 ± 4.04	61.1 ± 2.60	**0.015**
ALS (10^3/μL)	2,133 ± 473.3	2,272 ± 249.9	0.77
Lymphocyte (%)	18.3 ± 2.65	25.3 ± 1.88	**0.034**
Monocyte (%)	6.27 ± 1.22	11.9 ± 1.27	**0.006**
Eosinophil (%)	2.1 ± 0.98	1.33 ± 0.29	0.30
Basophil (%)	0.80 ± 0.45	0.39 ± 0.03	0.36
CK (U/L)	203.05 ± 72.7	41.8 ± 7.4	**0.04**
CK-MB (ng/mL)	24.2 ± 7.5	5.9 ± 1.3	**0.026**
hs-Troponin T (ng/L)	157.9 ± 58.6	16.3 ± 3.4	**0.028**
Pro-BNP (pg/mL)	5,240 ± 1,907	315,8 ± 184.7	**0.019**
CRP (mg/L)	111.8 ± 21.6	100.03 ± 14.6	0.64
ESR (mm/St)	59.09 ± 7.06	69.1 ± 5.5	0.26
PCT (ng/mL)	13.6 ± 7.1	0.78 ± 0.3	0.09
Ferritin (ng/mL)	1,715 ± 1,133	461.7 ± 193.8	0.28
Fibrinogen (mg/dL)	466.4 ± 30.9	475.8 ± 28.6	0.83
D-dimer (μg/mL)	5.75 ± 1.65	1.98 ± 0.31	**0.036**

Table 6. Comparison of electrocardiogram and echocardiogram findings between the patients with and without multisystem inflammatory syndrome in children (MIS-C) diagnosis

	MIS-C + (n = 22)	MIS-C - (n = 42)	p
Mean PR interval, (s)	0.17 ± 0.03	0.13 ± 0.02	**0.0001**
Prolonged PR, n (%)	3 (13.6%)	1 (2.4%)	0.11
Mean QTc interval, (s)	0.40 ± 0.006	0.39 ± 0.004	0.08
Prolonged QTc, n (%)	2 (9%)	1 (2.4%)	0.27
Mean QRS interval, (s)	0.07 ± 0.002	0.07 ± 0.001	0.73
ST-T variation, n (%)	1 (4.5%)	2 (4.8%)	0.73
Ventricular hypertrophy signs, n (%)	1 (4.5%)	1 (2.4%)	0.57
Arrhythmia signs, n (%)	2 (9%)	0 (0%)	0.11
Ejection fraction (%)	64.1 ± 1.68	71.8 ± 0.94	**0.0001**
Systolic dysfunction, n (%)	2 (9%)	0 (0%)	0.11
Normal systolic func., n (%)	2 (9%)	0 (0%)	0.11
Diastolic dysfunction, n (%)	15 (68.1%)	6 (14.2%)	**0.001**
Normal Diastolic func., n (%)	3 (13.6%)	2 (4.8%)	0.32
Valve insufficiencies, n (%)	1 (4.5%)	0 (0%)	0.34
Pericardial effusion, n (%)	2 (9%)	1 (2.4%)	0.27

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Table 7. Relationships between multisystem inflammatory syndrome in children (MIS-C), cardiac involvement status, biochemical parameters

	MIS-C + (n = 22)			MIS-C - (n = 42)			*a*-c**	*b*-d**
	Cardiac Inv. (+) (*n* = 18)[a]	Cardiac Inv. (-) (n = 4)[b]	p	Cardiac Inv. (+) (n = 16)[c]	Cardiac Inv. (-) (n = 26)[d]	p	p	p
CK (U/L)	237.9 ± 90.4	74.5 ± 20.6	0.37	50.6 ± 15.4	35.7 ± 6.8	0.33	0.06	**0.034**
CK-MB (ng/mL)	21.4 ± 7.1	36.8 ± 29.4	0.44	4.74 ± 2.6	6.5 ± 1.4	0.51	0.10	0.37
hs-Troponin T (ng/L)	148.1 ± 56.1	4.5 ± 2.6	**0.02**	7.5 ± 3.3	5.1 ± 2.1	0.53	**0.02**	0.90
Pro-BNP (pg/mL)	6,413 ± 2,302	550 ± 149.4	0.22	115.3 ± 29.3	427.2 ± 286.4	0.42	**0.01**	0.84
CRP (mg/L)	119.6 ± 25.2	76.6 ± 35.6	0.45	91.2 ± 26.8	105.2 ± 17.4	0.65	0.44	0.53
ESR (mm/St)	62.1 ± 8.31	46.2 ± 10.6	0.39	62.8 ± 8.4	72.2 ± 7.2	0.43	0.95	0.12
PCT (ng/mL)	15.5 ± 8.2	1.7 ± 0.4	0.51	0.3 ± 0.1	0.99 ± 0.47	0.34	0.09	0.58
Ferritin (ng/mL)	654.1 ± 252.9	7,730 ± 7,560	0.44	221.1 ± 67.2	582.1 ± 287.7	0.38	0.11	0.44
Fibrinogen (mg/dL)	477 ± 35.4	421.7 ± 64.7	0.49	432.6 ± 50.2	494.1 ± 34.8	0.33	0.46	0.44
D-dimer (µg/mL)	6.3 ± 1.9	3.1 ± 2.5	0.46	2.8 ± 0.5	1.58 ± 0.36	0.06	0.15	0.57

a: with MIS-C and with cardiac involvement, b: with MIS-C and without cardiac involvement, c: without MIS-C and with cardiac involvement, d: without MIS-C and without cardiac involvement.

Table 8. Relationships between multisystem inflammatory syndrome in children (MIS-C), cardiac involvement, and electrocardiogram and echocardiogram findings

	MIS-C + (n = 22)			MIS-C - (n = 42)			*a*-c**	*b*-d**
	Cardiac Inv. (+) (n = 18)[a]	Cardiac Inv. (-) (n = 4)[b]	p	Cardiac Inv. (+) (n = 16)[c]	Cardiac Inv. (-) (n = 26)[d]	p	p	p
Mean PR interval, (s)	0.17 ± 0.006	0.15 ± 0.02	0.13	0.14 ± 0.008	0.13 ± 0.004	0.28	**0.002**	0.40
Mean QRS interval, (s)	0.07 ± 0.002	0.06 ± 0.005	0.20	0.07 ± 0.002	0.07 ± 0.002	0.75	0.66	0.43
Mean QTc interval, (s)	0.39 ± 0.007	0.38 ± 0.009	0.63	0.42 ± 0.008	0.38 ± 0.003	**0.008**	**0.008**	0.12
Prolonged QTc, (s)	2 (11.1%)	0 (0%)	0.66	1 (6.25%)	0 (0%)	0.38	0.57	–
Prolonged PR, n (%)	3 (16.7%)	0 (0%)	0.53	1 (6.25%)	0 (0%)	0.38	0.60	–
ST-T variation, n (%)	1 (5.5%)	0 (0%)	0.81	2 (12.5%)	0 (0%)	0.14	0.58	–
Ventricular hypertrophy signs, n (%)	1 (5.5%)	0 (0%)	0.81	1 (6.25%)	0 (0%)	0.38	0.71	–
Arrhythmia signs, n (%)	2 (11.1%)	0 (0%)	0.66	0 (0%)	0 (0%)	–	0.49	–
Ejection fraction, (%)	63.3 ± 1.99	67.5 ± 1.65	0.35	72.8 ± 1.46	71.2 ± 1.22	0.41	**0.001**	0.26
Systolic dysfunction, n (%)	2 (11.1%)	0 (0%)	0.66	0 (0%)	0 (0%)	–	0.48	–
Diastolic dysfunction, n (%)	2 (11.1%)	0 (0%)	0.66	0 (0%)	0 (0%)	–	0.48	–
Valve insufficiencies, n (%)	15 (83.3%)	0 (0%)	0.091	6 (37.5%)	0 (0%)	**0.002**	0.07	–
Pericardial effusion, n (%)	3 (16.7%)	0 (0%)	0.74	2 (12.5%)	0 (0%)	0.14	0.61	–
Cardiac vegetation, n (%)	1 (5.5%)	0 (0%)	0.81	0 (0%)	0 (0%)	–	0.54	–
Coronary changes, n (%)	2 (11.1%)	0 (0%)	0.66	1 (6.25%)	0 (0%)	0.38	0.57	–

a: with MIS-C and with cardiac involvement, b: with MIS-C and without cardiac involvement, c: without MIS-C and with cardiac involvement, d: without MIS-C and without cardiac involvement.

high hs-Troponin T levels and no pathologic echocardiogram findings. One of the two patients with ST-T changes had high hs-Troponin T levels, while the other had normal hs-Troponin T levels and pericardial effusion in echocardiogram. These results showed that electrocardiogram changes were directly associated with cardiac involvement. In particular, interval changes such as prolonged PR and QTc intervals were observed in the absence of myocardial damage. Many studies in the relevant literature have shown a relationship between COVID-19 infection and electrocardiogram changes.[5,25,26]

All abnormal echocardiographic findings were observed exclusively in patients with cardiac involvement valvular insufficiency was much more common and EF values were significantly lower in the patient group with multisystem inflammatory syndrome in children compared to the patient group without multisystem inflammatory syndrome in children, according to the analysis of the correlations between echocardiographic results and the diagnosis of multisystem inflammatory syndrome in children in our study. Although the mean EF values were found to be lower in the group with multisystem inflammatory syndrome in children, only two patients in this group had EF values below the normal range. In their study conducted with paediatric patients, in their group of 294 patients with multisystem inflammatory syndrome in children, Cantarutti et al. identified pericardial effusion in 42 (14%) patients, left ventricular systolic dysfunction in 27 (9%), and coronary aneurysms in 16 (5.4%).[5] Çevik et al. reported in their study conducted with 70 paediatric patients that five (7.1%) patients had pericardial effusion, 20 (28.5%) had MI, five (7.1%) had left ventricular systolic dysfunction, and three (4.2%) had coronary artery dilation. The three patients with dilation in their coronary arteries were also in the group diagnosed with multisystem inflammatory syndrome in children.[26] Studies in the literature of paediatric COVID-19 cases have reported different rates of pathologic echocardiogram findings. In our study, the rate of pathologic valve insufficiency was higher in the patients with cardiac involvement compared with the rates reported in other studies. Furthermore, our results indicated that pathological valve insufficiency was directly associated with cardiac involvement in COVID-19, but EF changes were more associated with the severity of inflammation.

The most commonly reported symptoms among the 64 patients included in our study were fever (85.9%), diarrhoea (29.7%), rash (26.6%), and malaise (23.4%). This result was similar to those in the literature about presenting symptoms seen in children admitted to the hospital due to COVID-19.[26,27] The study findings revealed that the occurrence of malaise as an initial symptom in the group with cardiac involvement (Group 1) was significantly higher compared to the rate in the group without cardiac involvement. Moreover, the rates of rash and headache in the subgroups diagnosed with multisystem inflammatory syndrome in children were significantly higher than the rates in the subgroups not diagnosed with multisystem inflammatory syndrome in children.

Our findings indicated that in comparison to patients without multisystem inflammatory syndrome in children, those with multisystem inflammatory syndrome in children exhibited significantly elevated neutrophil counts and percentages, coupled with significantly lower lymphocyte and monocyte percentages. Like several other studies in the literature, our results also showed that having symptomatic COVID-19 infection and/or a severe clinical course of the disease was correlated with haematological changes such as elevated neutrophil counts and lower lymphocyte and monocyte counts.[13,21,28,29]

Our study had several limitations. It focused exclusively on symptomatic paediatric patients who experienced complications and were hospitalised with a diagnosis of COVID-19. Consequently, our findings are derived solely from data concerning paediatric patients with symptomatic COVID-19 infection. Additionally, the study did not assess the specific COVID variants in the patients, evaluate the treatments administered, or examine the patients' responses to treatment. Another constraint was the limited sample size, attributed to the study's cross-sectional nature.

Conclusion

In our research, we found that the primary indicator of cardiac involvement was the elevated levels of hs-Troponin T. Notably, prolonged PR and QTc intervals in electrocardiogram findings emerged as potential markers of cardiac involvement, even in the absence of other signs. Another noteworthy finding was the robust correlation between the severity of inflammation and cardiac involvement. It appears that assessing patients with elevated levels of inflammatory markers, in conjunction with their cardiac enzyme levels, electrocardiogram findings, and echocardiogram results, is crucial to avoid missing potential cardiac involvement.

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Competing interests. None.

Ethical standard. This study was in compliance with the "Declaration of Helsinki" and was approved by the Ethics Committee of Gazi University.

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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