Circulation

ORIGINAL RESEARCH ARTICLE

Acute Cardiovascular Manifestations in 286 Children With Multisystem Inflammatory Syndrome Associated With COVID-19 Infection in Europe

BACKGROUND: The aim of the study was to document cardiovascular clinical findings, cardiac imaging, and laboratory markers in children presenting with the novel multisystem inflammatory syndrome associated with coronavirus disease 2019 (COVID-19) infection.

METHODS: This real-time internet-based survey has been endorsed by the Association for European Paediatric and Congenital Cardiologists Working Groups for Cardiac Imaging and Cardiovascular Intensive Care. Children 0 to 18 years of age admitted to a hospital between February 1 and June 6, 2020, with a diagnosis of an inflammatory syndrome and acute cardiovascular complications were included.

RESULTS: A total of 286 children from 55 centers in 17 European countries were included. The median age was 8.4 years (interquartile range, 3.8–12.4 years) and 67% were boys. The most common cardiovascular complications were shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation. Reduced left ventricular ejection fraction was present in over half of the patients, and a vast majority of children had raised cardiac troponin when checked. The biochemical markers of inflammation were raised in most patients on admission: elevated C-reactive protein, serum ferritin, procalcitonin, N-terminal pro B-type natriuretic peptide, interleukin-6 level, and D-dimers. There was a statistically significant correlation between degree of elevation in cardiac and biochemical parameters and the need for intensive care support ($P<0.05$). Polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 was positive in 33.6%, whereas immunoglobulin M and immunoglobulin G antibodies were positive in 15.7% cases and immunoglobulin G in 43.6% cases, respectively, when checked. One child in the study cohort died.

CONCLUSIONS: Cardiac involvement is common in children with multisystem inflammatory syndrome associated with the Covid-19 pandemic. The majority of children have significantly raised levels of N-terminal pro B-type natriuretic peptide, ferritin, D-dimers, and cardiac troponin in addition to high C-reactive protein and procalcitonin levels. In comparison with adults with COVID-19, mortality in children with multisystem inflammatory syndrome associated with COVID-19 is uncommon despite multisystem involvement, very elevated inflammatory markers, and the need for intensive care support.

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Clinical Perspective

What Is New?

- Cardiac involvement is very common in children with multisystem inflammatory syndrome associated with coronavirus disease 2019 (COVID-19) infection.
- Inflammatory markers were significantly raised in most children, especially C-reactive protein, ferritin, procalcitonin, N-terminal pro B-type natriuretic peptide, interleukin-6 level, and D-dimer levels.
- Sixty-five percent of patients with pediatric multisystem inflammatory syndrome had evidence of previous infection with severe acute respiratory syndrome coronavirus 2 either by detection of a positive polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 nucleic acid or the detection of severe acute respiratory syndrome coronavirus 2 immunoglobulin M or immunoglobulin G antibodies.

What Are the Clinical Implications?

- Children with pediatric multisystem inflammatory syndrome should be monitored for shock, cardiac arrhythmias, pericardial effusion, and coronary artery dilatation: the 4 most common cardiovascular complications in our cohort.
- There is a statistically significant correlation between degree of elevation in cardiac and biochemical markers and the need of intensive care support.
- In comparison with adults, mortality in children with multisystem inflammatory syndrome associated with COVID-19 is uncommon despite significantly high inflammatory markers and multisystem involvement.

The first cases of coronavirus disease 2019 (COVID-19) were reported in Europe on January 24, 2020.[1] The World Health Organization considered Europe the active center of the COVID-19 pandemic on March 13, 2020; the initial experience and expectation was that children would be minimally affected in comparison with the widespread morbidity and mortality seen in adults. However, toward the end of April, alerts were issued across Europe because of the unexpected emergence of a novel inflammatory shock syndrome in children, who were presenting with persistent fever, elevated laboratory markers, and acute cardiovascular compromise.

On April 27, Public Health England circulated a clinical alert, followed soon after by preliminary case definitions, first from the UK Royal College of Paediatrics and Child Health: pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and subsequently by the Centers for Disease Control and Prevention: multisystem inflammatory syndrome in children (MIS-C).[2]

This new syndrome shares clinical features with other well-known syndromes such as viral myocarditis, Kawasaki disease (KD), Kawasaki shock syndrome, and toxic shock syndrome. Common features include persistent fever, elevated inflammatory markers, circulatory shock, and cardiac involvement. Cardiac involvement may include rhythm disturbance, depressed myocardial function, valvar regurgitation, and coronary artery inflammation. This variability in clinical presentation poses a diagnostic challenge, because most of the laboratory tests for differential diagnosis of these acute cardiovascular inflammatory syndromes may not be immediately available at admission, sensitivity is often low, and, specifically for KD, there is currently no single diagnostic test. This limits the treating clinicians to using overlapping clinical criteria, making it difficult to optimally individualize disease management.

The World Health Organization urged collection of standardized data describing clinical presentations, severity, outcomes, and epidemiology.[3] In April 2020, we initiated an online survey supported by the Association for European Paediatric and Congenital Cardiology, targeting member cardiologists and cardiac intensivists across Europe. The survey was launched with the purpose of rapidly providing clinically useful data, focused on associated cardiovascular findings but also including basic laboratory features to guide clinicians in the early diagnosis and timely management of this novel acute cardiovascular inflammatory syndrome in children during the COVID-19 pandemic.

METHODS

We conducted a rapid-response, real-time audit of pediatric patients with symptoms consistent with the newly described MIS-C, admitted acutely to 55 participating European hospitals. We chose a sampling window of February 1 to June 6, 2020, to include the period of peak prevalence of COVID-19 in Europe and to allow rapid dissemination of results to practicing clinicians, in particular, those in countries yet to reach their COVID-19 peak. The survey was coordinated by the Working Groups for Cardiac Imaging and Cardiovascular Intensive Care from the Association for European Paediatric and Congenital Cardiology (AEPC). The study was approved by the local institutional review committee and subjects gave informed consent according to the principles of the Declaration of Helsinki. All patient data were deidentified with respect to dates of birth or dates of discharge or death. The registry is built and maintained as an electronic database housed at the Institute of Biomedicine in Seville, Spain. The data that support the findings of this study are available from the corresponding author on reasonable request.

Children presenting with persistent fever, inflammation (neutrophilia, elevated C-reactive protein), and evidence of cardiovascular involvement (shock, acute cardiac dysfunction),

who may also present with multiorgan dysfunction (respiratory, renal, gastrointestinal, or neurological), were included (Table 1). This may include children fulfilling full or partial criteria for KD. Inclusion criteria were broad to include centers using both the Royal College of Paediatrics and Child Health (pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2) and the Centers for Disease Control and Prevention (MIS-C) case definitions. Inclusion did not require proof of SARS-CoV-2 infection.

Patient data collection was divided into the following primary sections: patient demographics and preexisting comorbidities, family background, clinical presentation, laboratory findings, cardiac findings, pharmacological treatment, and outcomes. Ethnicity was defined using UK government groupings.[4] The laboratory parameters were collected as reported by the individual centers. Standard international normal ranges were used to decide the cutoff point whether laboratory markers were raised or not, and, for the echocardiography findings, *z* values were derived from the provided data.[5–7]

Management guidelines were not mandated, and centers were free to treat each patient according to local protocols.

Statistical Analysis

We used descriptive statistics to show the baseline demographic information of the participants. Continuous data were expressed as median and interquartile range (IQR) values. Categorical data were expressed as proportions (%). The study population was divided into 2 broad outcome groups: patients admitted to ward or to the intensive care unit. Comparison of continuous echocardiographic and laboratory test variables between groups were compared using the Mann-Whitney *U* test for independent samples. Categorical data were compared in cross tables and tested with the Pearson χ^2 test. Statistical analysis to compare continuous and categorical variables was performed where appropriate. A *P* value of <0.05 was chosen as cutoff for significance. Data were analyzed with SPSS (version 26.0).

Table 1. Acute Cardiovascular Inflammatory Syndrome Inclusion Criteria

Inflammatory syndrome
Persistent fever >38 °C*
Elevated laboratory markers of inflammation*
Associated multiorgan dysfunction†
Acute cardiovascular complications
Acute coronary artery involvement
Acute myocardial injury
Arrhythmias
Cardiogenic shock
Pericardial effusion
Thromboembolic complications

Children and adolescents (0–18 years) with Inflammatory syndrome: persistent fever AND elevated laboratory markers of inflammation AND any of the acute cardiovascular complications. Presence of associated multiorgan dysfunction is optional.

*Mandatory.

†Optional.

RESULTS

A total of 286 children, median age 8.4 years (IQR, 3.8–12.4; range, 1 month to 18 years), 194 boys (67.8%) and 92 girls (32.2%) were included (Table 2). Fifty-five centers from 48 cities and 17 European countries submitted data regarding children admitted to the hospital between February 1 and June 6 (Table I and Figure I in the Data Supplement). The peak incidence of admission was recorded from mid-April to mid-May 2020 (Figure).

Clinical Characteristics

A summary of the clinical presentation is presented in Table 3. Most patients were previously healthy: only 4 had congenital heart disease and 12 had an associated autoimmune disorder (Table II in the Data Supplement). All patients presented with persistent fever >38 °C in the days before admission; other common signs and symptoms included abdominal pain or diarrhea in 204 patients (71.3%), erythematous skin rash in 179 patients (62.6%), and conjunctival changes in 156 patients (54.5%). Shock was present in 115 (40.2%). Over half (56.6%, 162 patients) of the cohort required admission to intensive care during their hospital stay.

Table 2. Patients' Demographic Characteristics

Characteristics	Median	Interquartile range [P25–P75]	n	%
Age, y	8.4	[3.8–12.4]		
<1			21	7.3
1–5			86	30.1
6–10			75	26.2
11–18			104	36.4
Weight, kg	30	[15.6–50.3]		
Height, cm	132	[100–158]		
Body surface area, cm^2	1	[0.62–1.5]		
Sex				
Female			92	32.2
Male			194	67.8
Ethnicity				
White			161	56.3
Black			59	20.6
Asian			29	10.1
Mixed			17	5.9
Other			20	7.1
Congenital heart disease			4	1.4
Associated autoimmune disorder			12	4.2

Continuous variables expressed as median and interquartile ranges. Categorical variables expressed as total number of patients (n) and percentages (%).

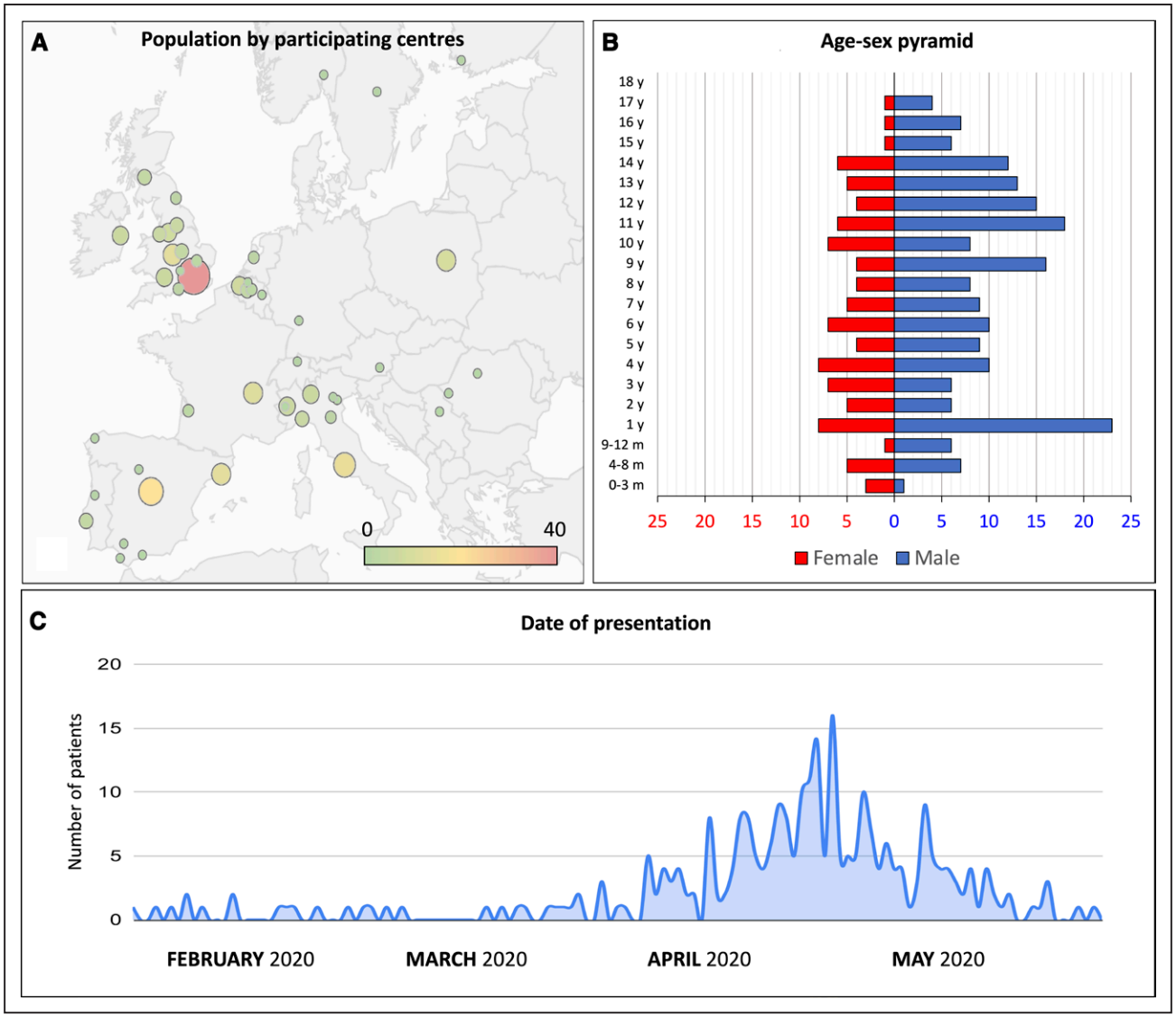

Figure. Study demographics.
A, Study population density across the 48 cities from 17 European countries. **B**, Age–sex pyramid distribution. **C**, Number of patients admitted to hospital during the European pandemic (February through May 2020).

Most of the children's families were reported as healthy; but 19.6% had persistent fever and 13.6% had respiratory tract infection. A positive test for SARS-CoV-2 on either polymerase chain reaction or antibodies against SARS-CoV-2 was reported in 14.7% of the family members (Table III in the Data Supplement).

Laboratory Investigations

Blood Test Results

The biochemical markers of inflammation were raised in the majority of patients on admission, and the most commonly performed parameters were C-reactive protein, serum ferritin, procalcitonin, and interleukin-6 level (see Table 4). C-reactive protein was collected on admission in 96% patients, of which 99% had abnormally elevated levels (median, 165 mg/L; IQR, 76–243 mg/L). Serum ferritin was measured in 77% of cases, of which 79% had elevated levels (median, 438 ng/mL; IQR, 420–846 ng/mL). Procalcitonin was measured in 51%, of which 96% had an increased level (median, 4.2 ng/mL; IQR, 1.3–6.1 ng/mL). A smaller number (12%) had interleukin-6 checked, and this was raised in 88%. For those requiring admission to the intensive care unit in comparison with those managed exclusively on the ward, all these inflammatory markers (C-reactive protein, ferritin, procalcitonin, and interleukin-6) were significantly ($P<0.05$) more abnormal. A detailed list of all laboratory investigations is included in Tables IV and V and Figures II–IV in the Data Supplement.

Cardiac biomarkers were elevated in a large proportion of cases. Common parameters checked were cardiac troponin T, B-type natriuretic peptide, and N-terminal pro-B type natriuretic peptide levels. Cardiac

Table 3. Patient's Clinical Presentation

Clinical presentation	n (%)
Fever >38 °C on admission	276 (96.5)
Abdominal-gastrointestinal: pain / diarrhea	204 (71.3)
Rash	179 (62.6)
Conjunctival injection	156 (54.5)
Oral mucosa hyperemia	116 (40.6)
Shock	115 (40.2)
Upper respiratory tract infection	97 (33.9)
Lymphadenopathy (cervical)	76 (26.6)
Extremities hyperemia/edema/desquamation	73 (25.5)
Lower respiratory tract infection	62 (21.7)
Neurological change	43 (15)

troponin T levels were recorded in 65% of cases, from which 93% were raised, with a median of 11 (IQR, 0.1–80.3 ng/mL). N-terminal pro-B type natriuretic peptide was measured in 53%, of which 94% had raised levels (median, 3299 pg/mL; IQR, 802–12 622 pg/mL). B-type natriuretic peptide was measured in a small proportion of cases (8%) and it was raised in 95% cases (median, 1180 pg/mL; IQR, 248–3510 pg/mL). In most patients, the peak biomarker abnormality was on admission, with no significant difference between these parameters on admission versus peak level during hospitalization.

Of the hematologic parameters reported, a significant number of patients had elevated D-dimers and a platelet abnormality. D-dimers were checked in 67% of patients, of whom 90% had very high levels with a median of 2599 ng/mL (IQR, 1244–4803 ng/mL). A platelet count was reported in 97% of patients, of whom 38% had abnormal platelet counts on admission (low in 26%, raised in 12%). Subsequently, during hospitalization, 19% had low platelet levels and 49% had raised platelet counts. A full blood count was recorded in 94% on admission, of which 56% had leukocytosis and 3% had leukopenia. During hospitalization, 73% had leukocytosis, whereas 7% had leukopenia.

Microbiological Investigations

Nasopharyngeal or oropharyngeal swab sampling for SARS-CoV-2 nucleic acid using reverse-transcriptase polymerase chain reaction assay was performed in 268 patients (93.7%), of which 90 patients (33.6%) had a positive swab. Two hundred sixty patients were screened for qualitative detection of SARS-CoV-2 antibodies (immunoglobulin M or immunoglobulin G) using lateral flow chromatographic immunoassay. Positivity for immunoglobulin M was confirmed in 41 patients (15.7%) and for immunoglobulin G in 116 patients (43.6%). Current or previous COVID-19 infection either by detection of a positive polymerase chain

Table 4. Laboratory Findings

Parameters	Ref value	Admission			Peak/most abnormal level during hospitalization		
		Abnormal n/total (%)	Median	Interquartile range [P25–P75]	Abnormal n/total (%)	Median	Interquartile range [P25–P75]
Biochemical parameters							
N-terminal pro B-type natriuretic peptide, pg/mL	<125	144/153 (94)	3299	[802–12 622]	159/171 (93)	3883	[955–12 354]
B-type natriuretic peptide, pg/mL	<24.5	21/22 (95)	1180	[248–3510]	29/33 (88%)	534	[48–2494]
Cardiac troponin (cardiac troponin T), ng/mL	<0.01	173/187 (93)	11	[0.1–80.3]	187/205 (91)	12	[0.1–132]
Procalcitonin, ng/mL	<0.15	139/145 (96)	4.2	[1.3–16.1]	133/147 (90)	3.6	[0.7–21.7]
Lactate dehydrogenase, U/L	110–144	197/198 (99)	344	[265–492]	196/198 (99)	367	[287–580]
Ferritin, ng/mL	50–200	176/222 (79)	438	[220–846]	187/223 (84)	478	[281–980]
C-reactive protein, mg/L	<1	274/276 (99)	165	[76–243]	260/269 (97)	175	[58–261]
Interleukin-6, pg/mL	5–15	30/34 (88)	147	[44–699]	41/56 (73)	61	[12–420]
Hematologic parameters							
Leukocytes, 10^3/μL	4500–10 000	>10 000: 152/270 (56) <4500: 7/270 (3)	10.9	[7.9–15.5]	>10 000: 188/259 (73) <4500: 18/259 (7)	14.2	[9.7–20.6]
Platelets, 10^3/μL	150–450	<150: 72/277 (26) >450: 32/277 (12)	214	[5–1047]	<150: 51/268 (19) >450: 131/268 (49)	446	[7–1364]
D-dimers, ng/mL	<250	173/192 (90)	2599	[1244–4803]	191/207 (92)	3126	[1478–6241]

Number of patients with abnormal values (n), percentages (%), and reference values are shown.

reaction for SARS-CoV-2 nucleic acid or the detection of SARS-CoV-2 immunoglobulin M or immunoglobulin G antibodies was confirmed in 186 patients (65%) in the cohort.

Eighty-seven patients were screened for viruses other than SARS-Cov-2. A total of 14 children had a positive screen for other viruses: adenovirus (2), herpes simplex virus type 1 (2), herpes simplex virus type 6 (1), respiratory syncytial virus (2), Epstein-Barr virus (2), parvovirus B19 (2), parainfluenza virus (2), and influenza virus (1). Eight of these patients also had a positive test to SARS-CoV-2.

Five patients had a positive serology for *Mycoplasma pneumoniae* (2 also with evidence of SARS-CoV-2 infection). See Table VI in the Data Supplement.

Chest X-ray

Chest X-ray was considered normal at admission in 133 patients (46.5%). The main abnormal findings were symmetrical infiltrates in 74 children (25.9%) and pleural effusion in 40 children (14%).

Abnormal ECG

An abnormal ECG was seen in 35.3% on admission, with return to normal during hospitalization in 72.4% (Table 5). Abnormalities seen include repolarization changes (abnormal ST- or T-wave segment) that were present in 63 patients (22%) and a prolonged PR interval present in 18 patients (6.3%).

Echocardiography

Echocardiography was performed on admission and during hospitalization in all patients. Echocardiographic parameters on admission and the worst values during hospitalization are summarized in Table 6 and in Table VII in the Data Supplement.

Tricuspid regurgitation was present in 17 patients (5.9%) at admission and in 12 patients (4.2%) during hospitalization. On admission, mitral regurgitation was mild in 109 patients (38.1%) and moderate in 12 patients (4.2%), decreasing to mild and moderate in 26.9% and 3.1%, respectively, during hospitalization. Pericardial effusion was detected in 80 patients (27.9%) at admission, reducing to 20.6% during hospitalization.

The most commonly performed assessments of left ventricular (LV) systolic function were M-mode–derived ejection fraction (EF) and fractional shortening, which were then classified using a qualitative scale.[8] Ejection fraction was impaired in 34% on admission, but recovered to normal in 80% during hospitalization. Regional wall motion abnormalities were described in 19 patients. For those requiring intensive care unit admission in comparison with those managed exclusively on the ward, systolic ventricular function was significantly

Table 5. Cardiac Findings: ECG, Computed Tomography, Magnetic Resonance Imaging

	On admission		During hospitalization	
Cardiac findings	n/total	(%)	n/total	(%)
ECG	286/286	(100)	286/286	(100)
Normal ECG	185	(64.7)	207	(72.4)
Abnormal ST- or T-wave segment	63	(22)	46	(16.1)
Prolonged PR interval	18	(6.3)	13	(4.5)
Bundle-branch block	11	(3.8)	10	(3.5)
Prolonged QT interval	9	(3.1)	13	(4.5)
Atrioventricular block	6	(2.1)	5	(1.7)
Tachyarrhythmias	5	(1.7)	5	(1.7)
Abnormal Q waves	3	(1)	2	(0.7)
Cardiac computed tomography			60/286	(21)
Coronary artery dilatation	–	–	16	(26.7)
Pleural effusion	–	–	12	(20)
Lung involvement	–	–	8	(13.3)
Pericardial effusion	–	–	5	(8.3)
Cardiac magnetic resonance imaging			42/286	(14.7)
T2 hyperintensity	–	–	14	(33.3)
Pericardial effusion	–	–	10	(23.8)
Positive first pass perfusion	–	–	1	(2.4)
Positive late gadolinium enhancement	–	–	6	(14.3)

Table 6. Cardiac Findings-II: Echocardiography Variables

Cardiac findings	On admission		During hospitalization	
	n/total	(%)	n/total	(%)
Two-dimensional and color Doppler				
Tricuspid regurgitation				
None	256/272	(94.1)	248/259	(95.8)
Mild	10/272	(3.8)	5/259	(2.1)
Moderate	6/272	(2.1)	5/259	(2.1)
Severe	0/272	(0.0)	0/259	(0.0)
Mitral regurgitation				
None	155/270	(57.3)	178/255	(69.9)
Mild	103/270	(38.1)	69/255	(26.9)
Moderate	11/270	(4.2)	8/255	(3.1)
Severe	1/270	(0.3)	0/255	(0)
Pericardial effusion				
None	192/266	(72.0)	198/249	(79.4)
Mild	66/266	(24.8)	45/249	(18.2)
Moderate	8/266	(3.1)	6/249	(2.4)
Severe	0/266	(0.0)	0/249	(0.0)
M-mode				
Reduced LV shortening fraction M-mode (<25%)	48/234	(20.6)	59/241	(24.5)
Reduced LV ejection fraction M-mode (<55%)	71/208	(34.2)	41/203	(20.2)
Reduced right ventricular tricuspid annular plane systolic excursion M-mode (z <–2)	46/138	(33.3)	32/143	(22.4)
Three-dimensional				
Reduced LV ejection fraction 3-dimensional (<55%)	11/35	(31.5)	17/45	(37.8)
Tissue Doppler imaging				
Reduced medial, s′ (z <–2)	6/72	(8.3)	6/82	(7.3)
Reduced medial, e′ (z <–2)	15/74	(20.3)	10/85	(11.7)
Reduced medial, a′ (z <–2)	3/58	(5.2)	3/74	(4.1)
Reduced lateral, s′ (z <–2)	13/71	(18.3)	4/88	(4.5)
Reduced lateral, e′ (z <–2)	25/82	(30.5)	33/98	(33.6)
Reduced lateral, a′ (z <–2)	6/61	(9.8)	4/79	(5.1)
Deformation				
Reduced LV global longitudinal strain	5/44	(11.4)	13/48	(26.5)

Number of patients with abnormal echocardiography parameters (n) and percentages (%). Parameters were normalized to z scores for M-mode[5] and Tissue Doppler imaging.[6] Systolic function was assessed by M-mode echocardiography (LV shortening fraction and right ventricular tricuspid annular plane systolic excursion; by tissue Doppler imaging, s′; or by deformation imaging: LV global longitudinal strain.[7] LV indicates left ventricular.

reduced; M-mode LV–fractional shortening (29% versus 33.5%), M-mode LV-EF (53% versus 63.1%), 3-dimensional LV-EF (51.5% versus 63%), and right ventricular tricuspid annular plane systolic excursion z score (–1.4 versus 0); see Figure V in the Data Supplement. Tissue Doppler Imaging and 3 dimensional EF systolic parameters did not differ significantly between admission or during hospitalization, or between the 2 outcome groups (see Table 6).

Echocardiographic evaluation of coronary arteries revealed dilatation (z>2) in any coronary artery in 69 patients (24.1%). The most affected arteries were the left main coronary artery (16.4%), left anterior descending (14%), right coronary artery (11.9%), and left circumflex (4.6%); see Table 7. During this short time frame (during hospitalization), most coronary artery abnormalities persisted; in only 5 patients was return to normality complete during hospitalization.

Table 7. Cardiac Findings-III: Echocardiography Coronary Arteries Evaluation

Findings	Admission				During hospitalization			
	Left main coronary artery	Left anterior descending	Left circumflex	Right coronary artery	Left main coronary artery	Left anterior descending	Left circumflex	Right coronary artery
Normal (z <2)	239 (83.6)	246 (86)	273 (95.5)	252 (88.1)	239 (83.6)	244 (85.3)	271 (94.8)	246 (86)
Ectasia (2≤ z <2.5)	25 (8.7)	15 (5.2)	7 (2.4)	15 (5.2)	22 (7.7)	11 (3.8)	8 (2.8)	16 (5.6)
Mild aneurysm (2.5≤ z <5)	18 (6.3)	20 (7)	5 (1.7)	13 (4.5)	18 (6.3)	21 (7.3)	6 (2.1)	17 (5.9)
Moderate aneurysm (5≤ z <10)	4 (1.4)	5 (1.7)	1 (0.3)	5 (1.7)	5 (1.7)	9 (3.1)	1 (0.3)	6 (2.1)
Giant aneurysm (z ≥ 10)	0 (0)	0 (0)	0 (0)	1 (0.3)	2 (0.7)	1 (0.3)	0 (0)	1 (0.3)

Number of patients with normal and abnormal echocardiography parameters (n) and percentages (%) in 286 children.

Cardiac Computed Tomography

Cardiac computed tomography was performed in 60 patients (21% of the study population). The main findings were the presence of coronary artery aneurysm (26.7%), pericardial (21%) or pleural effusion (20%), and lung involvement in 13.3%. Those cases with lung involvement were mainly described as bilateral pulmonary consolidation and ground-glass opacity.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) was performed in 42 patients (14.7% of the study population). Myocardial edema evaluated by T2 hyperintensity was present in 14 patients (33.3% of those with MRI). Pericardial effusion was present in 10 patients (23.8%), 9 patients with mild effusion and 1 with moderate effusion; positive first pass perfusion in only 1 patient (2.4%) and positive late gadolinium enhancement in 6 patients (14.3%). Of those, 5 patients had diffuse peri-epicardial late gadolinium enhancement, associated with high T2 hyperintensity and pericardial effusion. One patient presented with transmural enhancement in mid third septum. Pulmonary thromboembolism was not seen in any patient.

Other Imaging Findings

Abdominal ultrasound was performed in 159 patients (56%). Of those, it was normal in 97 patients (61%). Main findings were the presence of ascites (20.8%), lymphadenopathy (13.8%), ileitis (8.8%), and colitis (4.4%).

Treatment

Over three-fourths (78.3%) of the patients received intravenous immunoglobulin. Forty-five patients (15.7%) had additional biological immunomodulation (monoclonal antibodies), whereas 80 children (28%) were treated with intravenous steroids. Low-dose aspirin (3–5 mg·kg^{-1}·d^{-1}) was used in 212 patients (74.1%). Anticoagulation with heparin was reported in 108 patients (37.8%); 175 children (61%) received diuretics. Two hundred two patients (70.6%) received intravenous antibiotic treatment, and only 20 (7%) received antiviral treatment.

Eighty patients (30%) required inotropic support: 39 patients (13.6%) required dopamine (median, 5; IQR, 5–10), 80 patients (28%) required norepinephrine (0.1; IQR, 0.18–0.05), 63 patients (22%) required epinephrine (0.08; IQR, 0.03–0.1), 16 patients (5.6%) required dobutamine (median, 5; IQR, 5–10), and 74 patients (25.9%) required milrinone (0.5; IQR, 0.3–0.5).

Outcome

Clinical course was favorable in most of our cohort: 278 patients were discharged home (97.2%), with 7 patients (2.4%) still in the hospital at the closing date for inclusion. Mechanical ventilation was required in 44 patients (15.3%) with a median of 4 days (IQR, 2–5 days). Renal support with hemofiltration was required in 2 patients (0.7%) and peritoneal dialysis in 1 patient (0.3%). Extracorporeal membrane oxygenation support was required in 1 patient (0.3%). There was only 1 cardiac death; a 6-year-old boy with a 4-day history of fever and diarrhea who presented with shock and developed sustained ventricular tachycardia and ventricular fibrillation 1 day after admission. A 17-year-old boy developed dilated cardiomyopathy with reduced systolic function and is listed for heart transplantation. Median hospital stay was 10 days (IQR, 6–13 days) and a median intensive care unit stay was 5 days (IQR 3–7 days).

DISCUSSION

The incidence of clinically symptomatic COVID-19 infection in children is small (1%–2%)[9,10] in comparison with adults, with the vast majority of children developing only mild or no symptoms. However, during the current

pandemic, a novel MIS-C has been reported, arising weeks after the peak incidence of COVID-19 infection in adults. These children were commonly reported to have no evidence of active current COVID-19 infection, with multisystem inflammation proposed to be mediated by cytokine activation. Recent studies have shown that adult patients affected with COVID-19 may have associated cardiovascular complications,[1,9–12] including the potential for direct cardiomyocyte damage secondary to viral invasion or indirect myocardial injury attributable to acute severe inflammation, which may also disrupt the pulmonary endothelium.[13] Clinical manifestations in adults may include ECG change, myocardial enzyme elevation, or reduced cardiac output with clinical shock or quantifiable changes on cardiac imaging, predominantly echocardiography.[1,9–12]

Children with MIS-C have been reported to have cardiac involvement and clinical features overlapping with other acute inflammatory syndromes such as KD, toxic shock syndrome, and macrophage activation syndrome.[14–16] However, differences in the clinical presentation and laboratory findings suggest a distinct clinical syndrome in susceptible individuals.[2,17] When dealing with a novel disease, especially during a global pandemic emergency, clinical observations from a diverse geographical and population mix are crucial to further refine the case definition and develop management strategies, initially from expert consensus and hopefully later from controlled trials. Hence, we sought to rapidly benchmark the main cardiac findings in children and young adults across Europe.

The pathogenesis of KD remains unknown, but there is evidence of an associated viral infection, including by the coronavirus family.[18–20] The cytokine storm in KD can resemble macrophage activation syndrome or hemophagocytic lymphohistiocytosis[15] and has been reported recently in SARS-CoV-2 infection.[16] In patients with acute KD, endomyocardial biopsy has demonstrated histological features of cellular infiltration and edema, suggesting that the inflammation in KD is not just within coronary arteries, but represents a pancarditis.[21] However, unlike viral myocarditis, this inflammation has not translated into myocardial necrosis with significant elevation of troponin-I level.[22] In contrast, in our series, 93% of patients had raised troponin levels suggesting significant myocardial injury.

Kawasaki shock syndrome occurs in 2% to 7% of patients with KD,[23,24] and is characterized by sustained hypotension or clinical signs of low cardiac output,[25] as a result of decreased systolic function and vasoplegia.[17] Echocardiographic signs of myocardial injury improve after the acute phase and resolve more quickly in patients who have received intravenous immunoglobulins.[26] Normalization of systolic function is typically observed during long-term follow-up; however, more subtle echocardiographic abnormalities (strain, diastolic function) may persist.[27]

An initial case series[14] of this new clinical entity reported a 30-fold increase in the incidence of KD-like illness during the current pandemic, but these cases differed from their historical KD cohort; the patients were older, had multisystem involvement including markers of myocardial injury, and most showed evidence of seroconversion to SARS-CoV-2. A further case series of 35 febrile children with multisystem inflammation temporally associated with SARS-CoV-2 infection[17] described left ventricular dysfunction in all involved children, but with a rapid resolution and only mild-to-moderate troponin rise, suggesting that the mechanism of heart failure was not consistent with typical myocarditis. In a larger multicenter study of 58 children,[2] laboratory and epidemiological differences between MIS-C and KD or KD shock syndrome further supported a distinct clinical syndrome.

In our cohort of 286 children and young people, we obtained data from 55 centers across 17 European countries contributing specific cardiac and laboratory data, which showed a very high incidence of myocardial involvement (93%), shock (40%), and arrhythmia (35%). All patients had elevated inflammatory markers and the sickest patients, requiring admission to the intensive care unit, had significantly higher levels than those managed exclusively on the ward ($P<0.05$). The incidence of arrhythmias in our cohort of hospitalized children was higher (35%) than the incidence of adults hospitalized with COVID-19 infection (16%).[10,28] The pathogenesis of the arrhythmias remains unclear and may relate to inflammation, electrolyte disturbances, or myocardial injury.

Myocarditis is an inflammatory disease of the heart muscle with established histological and immunologic diagnostic criteria.[29] Pathophysiology is related to the combination of direct virus-mediated myocardial damage and host immune activation.[30] In our series, a viral screen was performed in only 30% of the cohort, with 14 cases having a positive screen to common viruses. Myocardial biopsy was not reported in any of our cohort. The consistent elevation in cardiac biomarkers, the prompt recovery to normal ventricular systolic function, and the associated multisystem involvement, and the absence simultaneously of active Covid-19 infection, argue against viral myocarditis as the primary disease process in our cases.

Cardiac imaging, primarily echocardiography, was fundamental to diagnosis and decision making, with reduced ventricular systolic function parameters associated with a higher likelihood of intensive care unit admission. Coronary artery involvement was seen 24% of cases, which is similar to the unselected KD population. There were no significant changes to coronary caliber *z* score during the hospital stay. Longer-term evaluation and follow-up will be needed similar to KD guidelines.

Limitations

This study is a clinical snapshot taken acutely during the emergence of a new disease state. We did not attempt to investigate the pathogenesis, mandate interventions, or provide management guidance. Given the absence of existing pathways of care for a previously unknown condition, and the multicenter nature of the survey, there is significant variability in the presentation and data recorded. Because of the small numbers submitted by some centers, we have not extrapolated results to describe distribution across countries. As more data emerge, it is hoped that the agreed on management guidelines will be clarified, providing an opportunity to study treatment interventions and pathophysiology in more detail over a longer time period. We also acknowledge that data were collected from many different laboratories across many centers that may have different analytical methods and normal ranges. However, given the significant abnormalities reported in the critical laboratory parameters, minor variation in laboratory ranges should not alter the underlying definition of abnormality. Reporting multicenter data from multiple countries and different populations is a major strength of this study. Regarding the echocardiography, we have assumed a high level of expertise in performing detailed echocardiograms including coronary artery views in sick children, but acknowledge that, in some patients, because of size, limited sonographic windows, or critical illness, a complete data set of all coronary arteries may not have been obtainable. We have assumed that coronary arteries not mentioned as abnormal were presumed to be normal. This assumption may lead to a smaller percentage of reported coronary abnormalities.

We also acknowledge that our study was conducted while the multiple case definitions were still evolving, and we focused primarily on those with abnormal cardiac findings: hence, children with MIS-C but with no cardiac involvement were not included.

Conclusion

The results of a rapid-response, large-scale multicenter pan-European survey focus on cardiac involvement in the newly described multisystem inflammatory syndrome in children associated with COVID-19, describe the features of cardiac dysfunction, and confirm elevated markers of inflammation and myocardial injury. There is a statistically significant relationship between the elevation of these markers and the need for intensive care support. To date, our data fortunately suggest that the number of reported cases of MIS-C has been low in comparison with the total population of children, notwithstanding the absence of comprehensive data on the number of children actually infected with COVID-19. The surge in MIS-C during April and May 2020 confirms the temporal association with the COVID-19 pandemic in Europe. Although the incidence of MIS-C appears to be falling in Europe, some parts of the world have not yet reached their local COVID-19 peak, and, therefore, children remain at risk of serious cardiac morbidities. Findings from our study will help in diagnosis and management of these children. Understanding the underlying cascade pathways and identifying children at higher risk is a priority. We urge all centers managing children and young adults to be vigilant and particularly so if a second wave of SARS-CoV-2 infection develops in the near future.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Study Group Collaborators and AEPC COVID-19 Rapid Response Team
Expanded Methods
Data Supplement Tables I–VII
Data Supplement Figures I–V

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