Multisystem Inflammatory Syndrome in Children: Tools for a Timely Diagnosis in the Emergency Department from an Italian Multicenter Survey

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Abstract: *Objective:* To assess the most frequent clinical features of Multisystem Inflammatory Syndrome in children (MIS-C) at presentation to the Emergency Department (ED) in a large multicenter cohort of patients, in order to define useful tools for a timely diagnosis. *Methods:* Clinical and laboratory characteristics were retrospectively reviewed for 210 MIS-C patients from18 Italian pediatric EDs. We assessed correlations between clinical and laboratory parameters and compared features of patients of different age (≤5 years and >5 years). *Results:* Fever was the main presenting symptom (100%), followed by conjunctivitis (46%), abdominal pain (44%), vomiting (41%) and diarrhea (39%). Forty-nine percent of children presented to the ED in critical or nearly critical condition. A higher prevalence of mucocutaneous involvement was found in younger children (69% *versus* 47%, $p<0.05$), whereas gastrointestinal symptoms were more common in children >5 years (62% *versus* 85%, $p<0.05$). Higher values of inflammatory markers (C-Reactive Protein, Ferritin, and Fibrinogen), Troponin T and Brain Natriuretic Peptide were related to abnormalechocardiography ($p<0.05$). No significant differences were detected in laboratory parameters between the two age groups, apart from ferritin, fibrinogen and troponin T, which resulted significantly lower in children ≤5 years. *Conclusions:* Apart from fever, the most common MIS-C manifestations at presentation to the ED are conjunctivitis, abdominal pain, vomiting and diarrhea. Younger children more frequently present with mucocutaneous involvement, while gastrointestinal manifestations are more common in older patients. These findings should be considered when MIS-C is suspected in the ED, in order to achieve a timely recognition of the condition.

Keywords: Systemic Inflammation, Pediatric, COVID-19, MIS-C.

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INTRODUCTION

Since January 2020, the world has been facing one of the most demanding health emergencies ever, the SARS-CoV-2 pandemic, which has today accounted for about 410 million cases and 5.8 million deaths [1]. Initial data analysis rapidly highlighted that children are less commonly affected by SARS-CoV-2 infection and generally experience a significantly less severe disease in comparison toadults [2].

Since April 2020, both in Europe [3, 4] and in USA [5] several pediatric patients presenting with Kawasaki Disease (KD) – like shock syndrome has been reported.

These patients showed pictures of variable severity up to multiorgan involvement and hyper inflammation, that on occasion required intensive care [6, 7].

Nasopharyngeal swabs for SARS-CoV-2 were predominantly negative while serology or recent medical history highlighted a previous SARS-CoV-2 infection, which had generally occurred in the preceding 2-8 weeks [8].

The CDC later defined this condition Multisystem Inflammatory Syndrome in Children (MIS-C) and the following diagnostic criteria were established: age <21 years, fever >24 hours; blood chemistry tests compatible with an inflammatory state; involvement of at least 2 organs or systems; severe clinical conditions requiring hospitalization; exclusion of other possible diagnoses, recent exposure (>4 weeks) to SARS-CoV-2 or positive nasopharyngeal swab or previous infection ascertained on serological examination [9].

Given the recent onset of this entity, a considerable amount of attention has been paid to the description of the disease in all its aspects, from the clinic to the laboratory and from instrumental tests up to management and therapy [10]. These studies have shown that early diagnosis and thereforeearly treatment is crucial for a better outcome [11].

As the clinical picture is highly variable and may develop gradually over several days, a correct differential diagnosis is challenging, particularly in the early stages of the disease. Indeed, sometimes MIS-C may show less severe manifestations, thus mimicking common febrile conditions of pediatric age, *e.g.*, Rotavirus gastroenteritis, infectious mononucleosis or Streptococcal pharyngitis, with consequent diagnostic delay [12].

The aim of the present study is to assess the most frequent clinical features of MIS-C at presentationto the Emergency Department (ED) in order to provide clinicians with useful tools for a timely recognition of the condition. The secondary aim was to determine if a specific age-group was associated with a different clinical and laboratorial presentation. This would allow a prompt diagnostic approach warrant a better therapeutic management of these patients, thus avoiding delays and possible life-threatening complications in affected children, but also unnecessary hospitalizations and diagnostic tests in non-MIS-C patients.

MATERIALS AND METHODS

We retrospectively analyzed data of patients presenting to the Emergency Departments (ED) of the 18 participating Italian centers between April 2020 and June 2021. The only inclusion criterion was an ultimate diagnosis of MIS-C. Data collection was performed by means of an online database that was sent and discussed in advance with all participating centers. The Institutional ethics committee of each participating center approved the study.

Collected data included age, gender, ethnicity, and all the parameters recorded at admission to the ED, including vital signs, clinical signs and symptoms, laboratory and instrumental findings.

For all patients, personal and family history of SARS-CoV-2 infection was investigated, and past medical history was collected to highlight any comorbidities. Presenting signs and symptoms were collected with the following categorization: mucocutaneous, gastrointestinal, neurological, respiratory, cardiovascular and musculoskeletal involvement.

With regards to the laboratory tests, particular attention was paid to the parameters needed for MIS-C diagnosis: blood count, inflammatory markers (C-Reactive Protein - CRP, Erythrocyte Sedimentation Rate - ESR, Ferritin, Fibrinogen, D-Dimer) and markers of organ dysfunction (transaminases, albumin, BNP and troponin, creatinine, CPK, LDH). In order to demonstrate the ongoing or recent infection by SARS-CoV-2, patients underwent IgG and IgM testing and molecular nasopharyngeal swab for SARS-CoV-2 detection.

When available, findings from instrumental examinations were collected. The main tests performed

within 24 hours after admission to the ED were cardiac ultrasound, electrocardiogram, chest X-ray, chest and abdomen Computed Tomography (CT) scan, and abdominal ultrasound. The present study is still ongoing with a prospective patient recruitment period that will end in March 2022.

STUDY POPULATION

We enrolled subjects aged 6 months to 18 years, who attended the ED due to fever and/or signs and symptoms suggestive of MIS-C and enrolled only those with subsequent confirmed diagnosis of MIS-C. The diagnosis was made according to the CDC criteria [9].

STATISTICAL ANALYSIS

Demographic, clinical and laboratory features were compared between age groups (≤5 years and >5 years). Median values and interquartile ranges were calculated to compare continuous variables and numbers, percentages for categorical variables were used. Continuous variables were tested for normality with the Shapiro-Wilks test [13]. Non-parametric Wilcoxon's rank sum test for continuous variables and chi-square test and Fisher's test, as appropriate, for categorical variables were used. A p value <0.05, two tailed, was considered statistically significant. Analysis was performed on Stata Corp LLC Stata 13.0 (College Station, TX).

RESULTS

We retrospectively enrolled 215 patients from 18 participating centers. Of these, 5 children were excluded from the analysis, as MIS-C diagnosis was not confirmed. Demographic and clinical data of the remaining 210 children are summarized in Table **1**.

Geographic origin of recruited patients from the different Italian regions is depicted in Figure **1**.

All children were Caucasian, with males representing more than half of the study population. Median age was 7 years [3-10] with 81 children (41%) under the age of 5 years. All patients presented fever (100%), which had started at least 72 hours before admission in most patients. With the exception offever, abdominal pain and conjunctivitis were the most frequent complaints at presentation, followed by vomiting, diarrhea and maculo-papular rash.

Almost half of patients presented to the ED in severe condition warranting a high or very high priority label at the triage evaluation. Indeed, 45/210 (21%), 52/210 (25%) and 6/210 patients (3%) were in three, two and

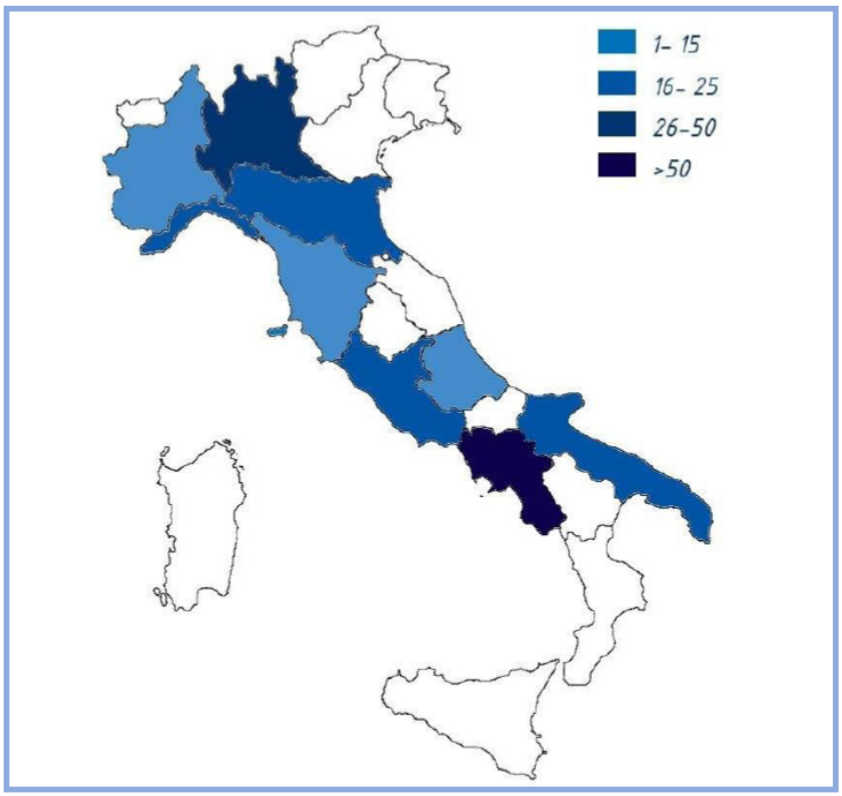

Figure 1: Geographic distribution of patients recruited.

Table 1:

	Patients		≤ 5 years	> 5 years	*p*-value
	obs.	n (%)/median (IQR)	n (%)/median (IQR)	n (%)/median (IQR)	
Age, yrs	210	7 (3-10)	3 (1-4)	9 (8-12)	
Gender, Male	210	131 (62%)	48 (55%)	83 (67%)	ns
Temperature, °C	203	38.1 (37.2-39)	38.1 (37.2-39)	38.1 (37.3-38.9)	ns
Heart Rate	188	130 (112-150)	140 (124-155)	123 (110-140)	**<0.05**
Respiratory Rate	85	28 (22-32)	28 (24-32)	28 (20-32)	ns
Oxygen saturation	193	98 (97-99)	98 (97-99)	98 (97-99)	ns
Systolic blood pressure	134	99 (90-108)	97 (90-103)	100 (91-109)	ns
Diastolic blood pressure	135	55 (50-65)	55 (50-60)	50(50-67)	ns
Capillary refill time, sec.	135	2.0 (2-2)	2 (2-2)	2.0 (2-2)	ns
General conditions	207				
Good		74 (36%)	32 (37%)	42 (35%)	ns
Discrete		94 (45%)	44 (51%)	50 (41%)	
Mediocre		33 (16%)	8 (9%)	25 (21%)	
Critical		6 (3%)	2 (2%)	4 (3%)	
Rash	210				
Absent		105 (50%)	57 (66%)	48 (39%)	**<0.05**
Maculo-papular		64 (30%)	31 (36%)	33 (27%)	ns
Urticarial		11 (5%)	7 (8%)	4 (3%)	ns
Vasculitic		7 (3%)	3 (3%)	4 (3%)	ns
Erythematous		34 (16%)	21 (24%)	13 (11%)	**<0.05**
Mucocutaneus involvement	210	118 (56%)	60 (69%)	58 (47%)	**<0.05**
Cheilitis		50 (24%)	30 (34%)	20 (16%)	**<0.05**
Strawberry tongue		19 (9%)	13 (15%)	6 (5%)	**<0.05**
Other		70 (33%)	31 (36%)	39 (32%)	ns
Changes to of the extremities	210	51 (24%)	29 (33%)	22 (18%)	**<0.05**
Ocular Involvement	210	104 (50%)	51 (59%)	53 (43%)	**<0.05**
Conjuntival injection		97 (46%)	46 (53%)	51 (41%)	ns
Uveitis		0	0	0	ns
Papilledema		0	0	0	ns
Other		13 (6%)	11 (13%)	2 (2%)	**<0.05**
Gastrointestinal involvement	210	159 (76%)	54 (62%)	105 (85%)	**<0.05**
Abdominal pain		92 (44%)	21 (24%)	71 (58%)	**<0.05**
Diarrhea		82 (39%)	22 (25%)	60 (49%)	**<0.05**
Vomiting		87 (41%)	28 (32%)	59 (48%)	**<0.05**
Hydrops of gallbladder		1 (0%)	0	1 (1%)	ns
Pancreatitis		1 (0%)	0	1 (1%)	ns
Other		13 (6%)	7 (8%)	6 (5%)	ns

(Table 1). Continued.

	Patients		≤ 5 years	> 5 years	*p*-value
	obs.	n (%)/median (IQR)	n (%)/median (IQR)	n (%)/median (IQR)	
Neurological involvement	210	107 (51%)	47 (54%)	60 (49%)	ns
Headaches		22 (10%)	4 (5%)	18 (15%)	**<0.05**
Irritability		33 (16%)	23 (26%)	10 (8%)	**<0.05**
Meningism		7 (3%)	4 (5%)	3 (2%)	ns
Altered mental state		6 (3%)	3 (3%)	3 (2%)	ns
Asthenia		49 (23%)	15 (17%)	34 (28%)	ns
Other		5 (2%)	1 (1%)	4 (3%)	ns
Respiratory Involvement	210	50 (23%)	16 (18%)	34 (28%)	ns
Cough		24 (11%)	7 (8%)	17 (14%)	ns
Dyspnea		10 (5%)	3 (3%)	7 (6%)	ns
Tachypnea		12 (6%)	4 (5%)	8 (7%)	ns
Lobar pneumonia		4 (2%)	1 (1%)	3 (2%)	ns
Interstitial lung diseases		5 (2%)	3 (3%)	2 (2%)	ns
Other		12 (6%)	3 (3%)	9 (7%)	ns
Cardiac Involvement	210	98 (47%)	37 (43%)	61 (50%)	ns
Myocarditis		37 (18%)	12 (14%)	25 (20%)	ns
Pericarditis		15 (7%)	2 (2%)	13 (11%)	**<0.05**
Valvular regurgitation		35 (17%)	13 (15%)	22 (18%)	ns
Coronary dilatation (2-2,5mm)		16 (8%)	9 (10%)	7 (6%)	ns
Coronary aneurysm (>2,5mm)		8 (4%)	6 (7%)	2 (2%)	ns
Heart failure		22 (10%)	6 (7%)	16 (13%)	ns
Hypotension		15 (7%)	3 (3%)	12 (10%)	ns
Shock		1 (0%)	1 (1%)	0	ns
Cardiac arrest		0	0	0	
Hepatomegaly	210	7 (3%)	0	7 (6%)	**<0.05**
Splenomegaly	210	6 (3%)	1 (1%)	5 (4%)	ns
Lymphadenopathy	210	44 (21%)	23 (33%)	15 (12%)	**<0.05**
Chest Pain	210	10 (5%)	0	10 (8%)	**<0.05**
Muscoloskeletal involvement	210	32 (15%)	8 (9%)	24 (20%)	**<0.05**
Arthritis		1 (0%)	0	1 (1%)	ns
Arthralgia		17 (8%)	5 (6%)	12 (10%)	ns
Myalgia		17 (8%)	3 (3%)	14 (11%)	**<0.05**
other		7 (3%)	3 (3%)	4 (3%)	ns
Oxygen supplementation	210	11 (5%)	3 (3%)	8 (7%)	ns

one priority categories respectively, according to the Emergency Severity Index [14]. With regards to the personal history of SARS-CoV-2 infection, only 68 patients reported recent infection (32%), but 90% of the study population had positive IgG, with the remaining 10% showing positivity for both IgM and IgG. Twenty-three patients (11%) had positive RT-PCR for SARS-CoV-2 on nasopharyngeal swab.

Comparison between the two age groups (age ≤ 5 years *versus* age > 5 years) showed a higher prevalence of mucocutaneous involvement in younger children (p <0.05), whereas gastrointestinal symptoms were more common in children older than 5 years (p <0.05) (Figure **2**).

Patients younger than 5 years presented less frequent heart involvement than older children, and the most common abnormalities are described in Figure **3**. In accordance with this finding, patients older than 5 years presented significantly higher troponin T and H levels (p <0.05).

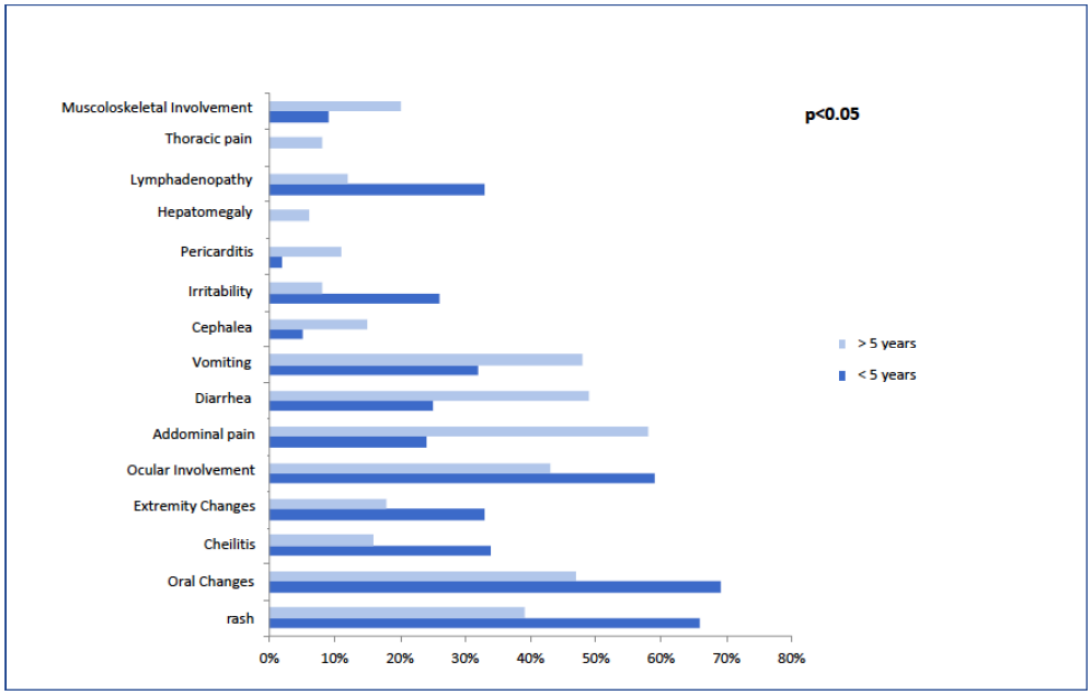

Figure 2: Comparison of clinical features between the two age groups.

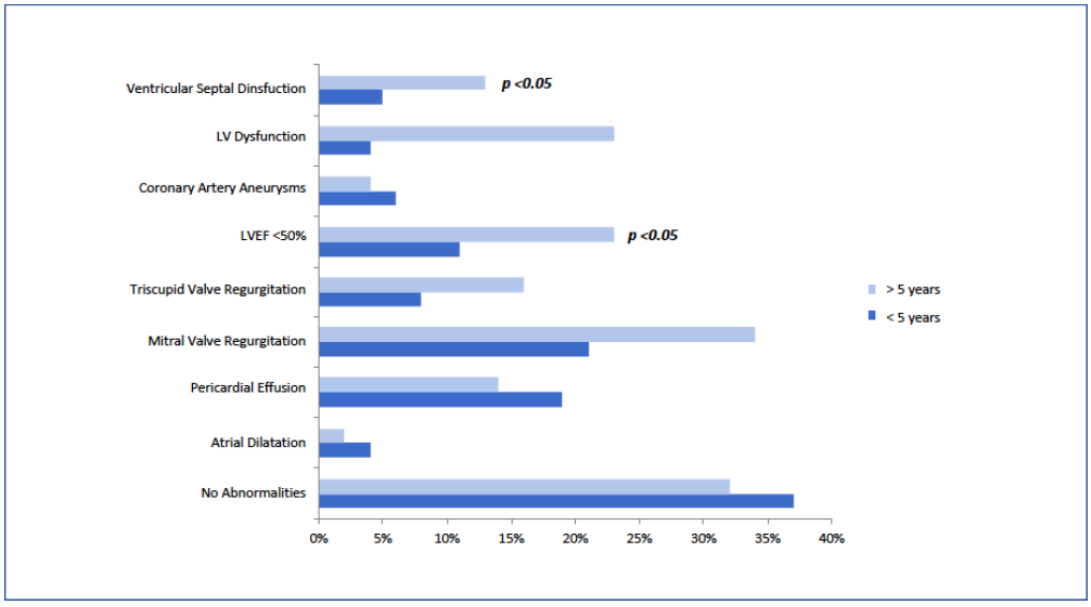

Figure 3: Comparison of the main heart cardiac abnormalities between the two age groups.

Table 2: Laboratory Data of the Study Population

	Patients		≤ 5 years	> 5 years	*p*-value
	obs.	median (IQR)	median (IQR)	median (IQR)	
WBC count (RR 5-15.5 x 10^3/µL)	207	10000 (7280-14150)	11985 (8040-16170)	9180 (7000-12310)	**<0.05**
Lymphocyte count (R.R.1.3 – 8.5 x 10^3/µL)	197	1070 (690-2000)	1990 (1250-3420)	860 (565-1150)	**<0.05**
Neutrophil count (R.R.1.3 – 8.5 x 10^3/µL)	207	7850 (5590-11210)	8480 (5785-12120)	7398 (5360-10510)	**<0.05**
Platelet count (R.R. 140 – 440 x 10^3/µL)	207	197 (146-271)	230 (182-335)	181 (135-228)	**<0.05**
Hemoglobin (R.R. 10.5 – 14 g/dL)	202	11.7 (10,9-12,6)	11.2 (10.3-11.9)	12.0 (11.3-12.9)	**<0.05**
AST (R.R. 5 – 58 U/L)	207	36 (26-57)	36.5 (28.0-53.0)	36.0 (26.0-58.0)	ns
ALT (R.R. 8 – 40 U/L)	207	27 (17-53)	26 (17-46)	28 (17-54)	ns
CK (R.R. 24 – 170 U/L)	178	62 (38-121)	61 (40-97)	64 (37-139)	ns
LDH (R.R. 300-550 U/L)	191	326 (266-491)	354 (282-502)	322 (255-436)	ns
Creatinin (R.R. 0.3 – 0.53 mg/dL)	205	0.47 (0.40-0.60)	0.39 (0.30-0.47)	0.54 (0.46-0.69)	**<0.05**
Blood urea (R.R. 10-38 mg/dL)	172	23.5 (18-32.5)	22 (17-28)	25 (19-35)	ns
Total bilirubin (R.R. 0.1-1.10 mg/dL)	153	0.49 (0.35-0.61)	0.40 (0.30-0.59)	0.50 (0.40-0.76)	ns
Amylase (R.R. 10-80 U/L)	109	31 (19-49)	30.5 (12.5-47.0)	32.0 (21.0-54.0)	ns
Lipase (R.R. 13-60 U/L)	60	30.5 (13-72.5)	27 (11-50)	34 (18-93)	ns
Sodium (R.R. 135-145 mEq/L)	208	133 (131-136)	133 (131-136)	133 (130-136)	ns
Potassium (R.R. 3.4-5.5 mEq/L)	203	4 (3.7-4.4)	4.2 (3.8-4.6)	4,0 (3.6-4.2)	**<0.05**
Chlorine (R.R. 96-115 mEq/L)	172	98 (95-101)	98 (95-101)	98 (95-100)	ns
Albumin (R.R. 3.4 – 4.8 g/dL)	173	3.4 (2.9-3,.9)	3.2 (2.8-4.0)	3,6 (3.0-3.9)	ns
Triglycerides (R.R. 35-90 mg/dL)	122	162 (117-226)	170 (114-225)	154 (122-227)	ns
C-RP (R.R. < 5 mg/L)	210	126 (83-210)	126 (73-200)	128 (90-213)	ns
Procalcitonin (R.R < 0.5 ng/mL)	146	5.9 (1.7-29.9)	5.6 (1.5-23.0)	6.1 (1.8-32.4)	ns
ESR (R.R. < 20 mm/1h)	91	51 (35-65)	50 (31-65)	53 (44-66)	ns
Ferritin (R.R. 7 - 54 ng/L)	160	426 (219-697)	316 (172-520)	488 (257-913)	**<0.05**
Troponin T R.R.(0-15 ng/L)	75	23.3 (7.0-53.8)	10.0 (3.0-24.0)	31.5 (13.6-81.0)	**<0.05**
Troponin I (R.R. <20 ng/L	47	36.6 (5.0-100)	30.2 (5.0-100.0)	48.9 (5.5-100.0)	ns
Troponin HS (R.R.1-14 ng/L)	49	35.5 (4.0-257)	3.8 (1.0-19.0)	145.5 (11.0-1170.5)	**<0.05**
Myoglobin (R.R. 20-72 ng/mL)	34	23.1 (21.0-38.5)	30.1 (21.0-130.9)	21.7 (21.0-34.3)	ns
Pro-BNP (R.R.<125 pg/mL)	90	1304 (249,2-4032)	2118 (364-5125)	960 (138-3424)	ns
BNP (R.R. 0 - 100 pg/mL)	63	179 (65-745)	147 (68-496)	203 (58-763)	ns
PT/INR ratio (R.R.0.8-1.20)	142	1.18 (1.07-1.28)	1.11 (1.02-1.26)	1.20 (1.12-1.30)	**<0.05**
Fibrinogen (R.R. 180 – 400 mg/dL)	185	575 (480-698)	547 (481-657)	610 (469-700)	**<0.05**
D-dimer (R.R. 0 – 270 ng/ml)	170	2378 (1120-4120)	2350 (1147-4300)	2406 (1076-3999)	ns

WBC, white blood cells; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatin kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; BNP, brain natriuretic peptide; INR, Prothrombin time/International normalized ratio.

Laboratory data are summarized in Table **2**. Elevated inflammatory markers such as CRP, ferritin and procalcitonin were detected in most children [126 mg/L (83-210), 426 ng/mL (219-697), 5.9 ng/L (1.7-29.9), respectively]. Hypertransaminasemia and altered cardiac markers were less commonfindings.

Value of inflammatory markers (CRP, Ferritin, and Fibrinogen), Troponin T and BNP were higher and

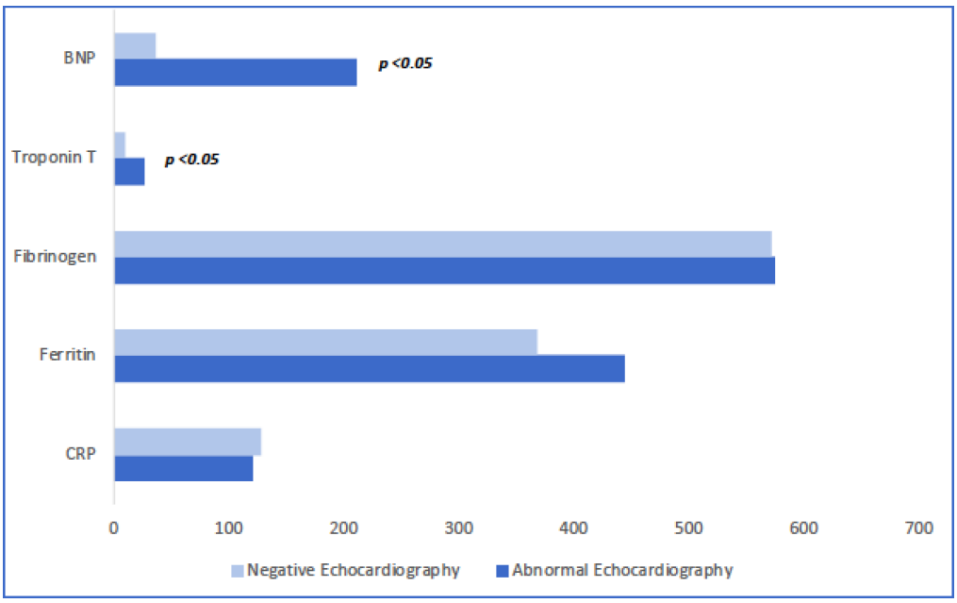

Figure 4: Correlation between laboratory tests and abnormal echocardiography.

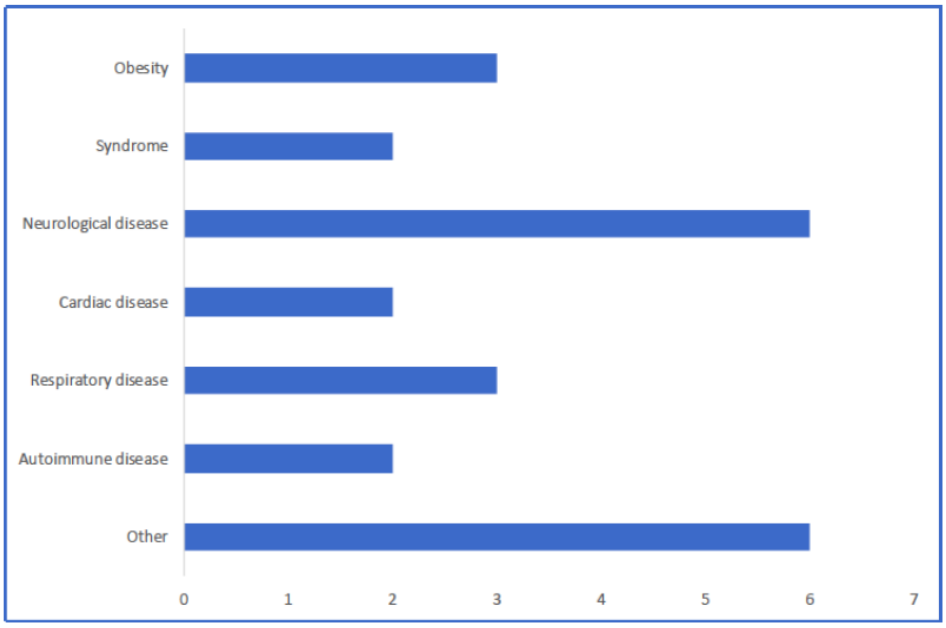

Figure 5: Comorbidities of 24 patients in study population.

related to abnormal Echocardiography ($p < 0.05$) (Figure **4**).

Twenty-four patients (11%) presented relevant comorbidities, reported in Figure **5**. A on-statistically significant correlation was found between the presence of comorbidities, increase of inflammatory markers and cardiac involvement.

DISCUSSION

The present multicenter study provides a detailed picture of a large population of MIS-C patients presenting to the EDs of several Children's Hospitals from all around Italy. Our data show that, at presentation to the ED, children with MIS-C are typically febrile, with a clinical picture that is not reassuring, and often present in nearly critical conditions, as demonstrated by the high or very high priority assigned at the triage evaluation to almost one third of the enrolled subjects. Of the several manifestations included in the diagnostic criteria, our findings showed that gastrointestinal involvement was largely prevalent at presentation, with abdominal pain, vomiting and diarrhea representing the leading

symptoms, affecting approximately 40% of subjects. Similarly, conjunctivitis and maculo-papular rash were highly frequent at presentation.

Interestingly, our data showed that clinical manifestations might vary significantly depending on the age of the child. Particularly, younger children resulted significantly more prone to presenting mucocutaneous and ocular involvement, changes of extremities and lymphadenopathy in comparison to patients older than 5 years. On the other hand, gastrointestinal and musculoskeletal systems were more frequently affected at presentation in older patients. No significant differences were detected in laboratory parameters between the two age groups, with particular reference to the main inflammatory markers, *i.e*., CRP, procalcitonin and ESR. Nevertheless, children aged 5 years or less showed significantly lower values of ferritin, fibrinogen and troponin T.

Our findings are only partially in line with previous reports of MIS-C patients assessed at presentation to the Pediatric ED, even though comparisons with other studies are limited by several factors. First, the large number of recruited patients partially limits the comparison with findings from smaller populations. In addition, the evolving course of the SARS-CoV-2 pandemic in the last two years has determined a progressive change of children's involvement, thus also affecting MIS-C epidemiology. Therefore, reports of the first cases described in 2020, particularly those regarding early manifestations of the condition, are barely comparable to more recently published studies, as clinicians' awareness of this condition and their ability to recognize and treat it have deeply improved. Notwithstanding these limits, the comparison of our population with a previous report of 34 MIS-C children of similar age confirms that approximately 50% of patients present to the ED with some degree of cardiac involvement often warranting intensive care [15]. Similarly, percentages of children with gastrointestinal manifestations at presentation overlap in the two populations [15]. Such symptoms may sometimes mimic surgical conditions such as acute appendicitis, as highlighted by a large multicenter Latino-American study which reported several cases of children who mistakenly underwent surgery due to MIS-C presenting with severe abdominal pain [16].

On the other hand, unlike Sethuraman and coworkers, who reported conjunctivitis only in 26% of patients, we found this typical ocular involvement in 46% of our children.

A relevant aspect that emerges from our analysis is the different clinical picture at presentation in children younger or older than 5 years. The higher frequency of mucocutaneous involvement, the less common occurrence of gastrointestinal manifestations, and the different pattern of cardiac disease would suggest that, in comparison to older children, MIS-C below 5 years, at least with regards to its early manifestations, shares more overlapping aspects with KD [17].

Despite several phenotypic similarities between MIS-C and KD, it has been clarified that they are two different conditions, with a variable degree of hyperinflammation and dysregulated immune responses [18, 19]. It has been hypothesized that the activation of the innate and adaptive immune responses underlying the two diseases is driven by a number of factors depending on both triggering pathogens and host conditions [20]. To what extent each of these factors contributes to the expressionof the clinical manifestations of MIS-C and KD is still unclear, but it is likely that, among the host factors, immune-system immaturity and intestinal microbiota, both age-dependent variables, play a pivotal role [21]. Therefore, as KD typically affects children below 5 years, one could speculate that these age-dependent host factors contribute to make MIS-C manifestations in this age range more similar to KD.

Another important finding of our study is that more severe laboratory abnormalities at presentation are significantly associated with cardiac impairment. This observation is likely to entail practical implications. First, since cardiologists with pediatric expertise are not immediately available in all ED, heart ultrasound is not always feasible. Therefore, particularly in limited-resource settings, knowing that higher inflammatory markers at presentation may be associated with a higher risk of cardiac involvement can help the attending clinician in assessing the urgency of an appropriate imaging, the opportunity to refer the patient to a tertiary care center, or even to inform a treatment strategy. Although the best therapeutic approach and its impact on outcomes have not been defined yet, most experts support the association of both immunoglobulins and steroids, particularly in severe cases, such as MIS-C with cardiac involvement [22].

Our study also highlights that the clinical presentation of this condition is extremely unspecific and a previous SARS-CoV-2 infection, which can somehow help the clinician in suspecting MIS-C, was

known in only one third of cases. These findings suggest that clinicians should have a high index of suspicion, particularly during periods of wide viral circulation in the community. On the other hand, it is important to stress that while some clues can suggest a diagnosis of MIS-C, other conditions including severe bacterial infections may have a similar presentation and should be ruled out, as a misdiagnosis may lead to delayed treatment with potentially life-threatening consequences. Indeed, reports of meningitis and other severe bacterial infections misdiagnosed as MIS-C have beendescribed [23, 24].

Our study has both strengths and limitations. As mentioned above, its multicenter design has allowedthe achievement of the largest sample size among studies assessing MIS-C patients at presentation published so far. Nevertheless, it is limited by its retrospective nature and by the lack of data regarding progression of the disease after presentation to the ED and response to treatment, even though these evaluations were beyond the aims of the study.

Clinicians' interest in the timely recognition and treatment of MIS-C is progressively growing. Daily experience in the management of these patients suggests that prompt treatment modulated on the severity of clinical manifestations may prevent the progression of the inflammatory process limitingthe risk of life-threatening complications and the need for intensive care. For this reason, Brisca and coworkers have recently proposed a severity assessment tool that stratifies patients in four classes with increasing levels of clinical impairment [25]. Based on such an assessment tool, they developed a multistep antinflammatory treatment protocol in which therapeutic interventions are modulated ona clinical severity score [25]. In this scenario, our findings provide a wide overview of the most common clinical manifestations of MIS-C patients presenting to the ED, and highlight the relevance of age as a factor affecting the more frequently involved systems. This will hopefully help an increasingly accurate and timely recognition of these patients in emergency settings, which has proven essential to improve their clinical outcomes.

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