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Multisystem Inflammatory Syndrome in Children (MIS-C) Associated With COVID-19 Infection in Morocco

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Abstract

Introduction. This study aims to describe the clinical and paraclinical characteristics of Multisysteminflammatory syndrome in children (MIS-C). *Methods*. A retrospective study encompassing 52 children diagnosed with MIS-C according to the World Health Organization criteria, over a 3-year period at Abderrahim Harrouchi Hospital in Morocco. *Results*. The median age was 6 years (IQR: 1-14), with a sex ratio of 1.16 (28 boys and 24 girls). Clinical manifestations were predominantly characterized by fever in all cases (100%), respiratory and gastrointestinal symptoms in 30 cases (58%) and 23 cases (44%) respectively, and shock in 9 cases (17%). We noted a myocarditis in 6 cases (12%). The treatment comprised intravenous human Immunoglobulin combined with methylprednisolone in all patients (100%). *Conclusion*. The characteristics of our MIS-C patients were similar to those in the literature, but more studies are needed to confirm these results.

Keywords
MIS-C, children, COVID-19

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Introduction

The SARS-CoV-2 virus, responsible for the 2019 coronavirus disease (COVID-19), has notably exhibited high transmissibility, severity, and fatality rates among adults.[1,2] However, this infection is typically benign in children. The rapid global spread of COVID-19 in early 2020 led to its classification as a pandemic by the World Health Organization (WHO)[3] in March of that year. Subsequently, several publications began documenting a severe inflammatory disease temporally linked to COVID-19 infection in children.[1] This newly nosological entity is referred to as "Pediatric Inflammatory Multisystem Syndrome" (PIMS) by the British and Europeans or "Multisystem Inflammatory Syndrome in Children" (MIS-C) by the Americans.[1,2] MIS-C developed 4 to 6 weeks after SARS-CoV-2 infection, suggesting that the virus may be a trigger for genetically predisposed individuals. While not all patients exhibit positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) results from nasal swabs, the majority demonstrate serological evidence or an epidemiological association with SARS-CoV-2 infection.[4] MIS-C profoundly affects multiple organ, encompassing the cardiac, gastrointestinal, hematological, dermatological, neurological, respiratory, and renal system. Although therapeutic strategies remain under debate, accumulating evidence suggests that the combination of immunoglobulins and intravenous corticosteroids yields superior outcomes compared to immunoglobulin monotherapy.[1,2] Our study endeavors to comprehensively document the epidemiological, clinical, paraclinical, and evolutionary characteristics of MIS-C in Morocco.

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Patients and Methods

Patients

We conducted a retrospective descriptive study including 52 Moroccan children with MIS-C for a 3 years period (March 2020-March 2023). The data were collected at the Infectious Diseases and Clinical Immunology Department of the Mother and Children's Abderrahim Harrouchi University Hospital in Casablanca. Each patient's information was meticulously recorded on a comprehensive data sheet, encompassing personal information, clinical manifestations, laboratory and radiological findings, treatment modalities, and outcomes. The sample size of 52 patients in our study was set on the basis of data availability during the defined period, the WHO[3] inclusion and exclusion criteria applied to our cohort, the principles of statistical power and precision of estimations.

Inclusion Criteria

The selection of patients for our study adhered to the MIS-C inclusion criteria as outlined by the WHO.[3] These criteria stipulate the following conditions for inclusion (all criteria must be met):

1. Age from 0 to 19 years,
2. Fever for ≥3 days,
3. Clinical signs of multisystem lesion (at least 2 of the following):
    - Rash, bilateral non-purulent conjunctivitis, or signs of inflammation of the skin and mucous membranes (oral, hands, or feet)
    - Hypotension or shock
    - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic data or elevated troponin/BNP)
    - Signs of coagulopathy (prolonged prothrombin time (PT); elevated D-dimer)
    - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Elevated inflammatory biomarkers (ESR, CRP, or Procalcitonin),
5. Signs of previous COVID-19 : Any of the following : Positive PCR of SARS-CoV-2/positive serological studies/positive antigen test/contact with a person with confirmed COVID-19.

Exclusion Criteria

Exclusion criteria for patient selection in our study encompassed the following :

1. Non-compliance with the inclusion criteria.
2. The presence of an obvious microbial cause of multisystem inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndrome.

Statistical Analysis

Descriptive statistics were employed to present the baseline demographic characteristics of the study participants. Quantitative variables were summarized using median values and interquartile ranges (IQR), while qualitative variables were presented as proportions (%). Data analysis were performed using Microsoft Excel version 14.0.

Ethical approval and informed consent. Institutional review board approval was required for this study by the institutional ethics committee of the University Hospital Center Ibn Rochd (CHUIR), as documented in reference number 2023/DOEHRSI/144, file number 22/23. We have obtained written informed consent from the legally authorized representatives of the minor subjects prior to study initiation.

Results. In our study, the median age was 6 years (IQR: 1-14 years), with a sex ratio of 1.16 (28 boys and 24 girls). The incidence of MIS-C in relation to the total number of COVID-19 cases hospitalized during the same period was 7%. COVID-19 contact was identified in 17 patients (33%). The median duration of hospital admission was 7 days (IQR: 3-10 days). Clinical manifestations included fever in 52 cases (100%), rash in 42 cases (80%), respiratory symptoms in 30 cases (58%), and gastrointestinal symptoms in 23 cases (44%). Shock was observed in 9 cases (17%), while neurological signs were present in 4 cases (8%). Many patients exhibited signs consistent with macrophage activation syndrome, such as splenomegaly and hepatomegaly in 9 cases (17%) (Table 1). The biological tests showed a positive SARS-CoV-2 PCR in 10 patients (19%). Serology was positive in 42 cases (81%), with anti-SARS-CoV-2.

Ig M positive in 25 cases (48%) and Ig G positive in 31 cases (60%). CRP was elevated in all patients (100%), and an increased erythrocyte sedimentation rate in 30 cases (58%). Furthermore, increased D-dimer levels were noted in 30 cases (58%), elevated Troponin in 21 patients (40%), and elevated Pro-PNB in 25 patients (48%). Interleukin 6 levels were elevated in 12 cases (23%) (Table 2). Echocardiography abnormalities were dominated by myocarditis with a reduced left ventricular ejection fraction (LVEF) (25%-30%) in 6 patients (12%) (Table 3). The management protocol entailed the

Table 1. Clinical and Evolutionary Signs in Our Study.

Clinical & Evolutionary signs	Number of patients (N = 52)	Percentage (%)
General signs		
Fever	52	100
Rash	42	80
Cheilitis	37	71
Raspberry tongue	37	71
Hands and feet edema	15	29
Skin desquamation	7	13
Non-purulent bilateral conjunctivitis	31	60
Laterocervical lymphadenopathy	11	21
Shock	9	17
Respiratory signs		
Cough	14	27
Dyspnea	15	29
Chest pain	1	2
Gastrointestinal signs		
Diarrhea	17	32
Vomiting	16	31
Abdominal pain	18	34
Hepatomegaly	9	17
Splenomegaly	9	17
Neurological signs		
Consciousness disorders	2	4
Meningeal syndrome	1	2
Seizure	1	2
Evolution		
Severe respiratory distress	4	8
Severe myocarditis	1	2
Severe shock	2	4
Macrophage activation syndrome	9	17

administration of intravenous human immunoglobulin (2 g/kg/day) in combination with intravenous methylprednisolone for all patients. Boluses of corticosteroids were additionally administered to 17 patients (32%), including 3 cases of myocarditis, 2 cases of acute kidney injury, 3 cases of disturbed consciousness, and 9 cases of macrophage activation syndrome. In instances where clinical signs and biological inflammatory syndrome persisted, 2 patients required a second course of immunoglobulin. All patients received ceftriaxone and acetylsalicylic acid at anti-platelet-aggregating doses. Those diagnosed with myocarditis were subjected to fluid restriction, diuretics, and the administration of a converting enzyme inhibitor (captopril). Moreover, 9 patients received dobutamine for shock management. Sixteen patients were transferred to intensive care, primarily due to severe respiratory distress in 4 cases (8%), severe myocarditis in 1 case (2%), severe shock in 2 cases (4%), and macrophage activation syndrome in 9 cases (17%). The short-term outcome was marked by acute kidney injury with anuria necessitating peritoneal dialysis, which ultimately resulted in a favorable outcome. Apyrexia was observed, on average, 2 days following the administration of immunoglobulins and corticosteroids. Thrombocytosis persisted in 3 patients, necessitating the continued administration of acetylsalicylic acid until platelet count normalization. During medium-term follow-up, of the 7 patients who underwent echocardiographic evaluation, 2 exhibited mild cardiac dysfunctions secondary to myocarditis, and 1 was diagnosed with a coronary aneurysm.

Discussion

COVID-19 infection has rapidly spread worldwide since it's identification in China at the end of 2019. Initially, children were relatively spared compared to adults.[2,5,6] The Incidence was estimated at 1.7%.[7] The true incidence remains unknown, as most children with COVID-19 are described as asymptomatic or with mild to moderate symptoms during the acute phase of infection.[7] However, since April 2020, several centers globally have reported children with an unexplained inflammatory syndrome linked to COVID-19. It was detected in Europe, specifically in France, Italy[8-11] and also by other American and English series[12,13] (Table 4). MIS-C is a rare affection worldwide. The number of affected patients remains very limited (1/100 000).[6,14] The incidence of MIS-C in relation to SARS-CoV-2 infection is challenging as SARS-CoV-2 infection in children are often asymptomatic and many countries do not systematically collect data on MIS-C in registries. Ooms et al.[15] detected an incidence of MIS-C at 7.2%. This incidence is close to the data reported in our study. Ethnic predisposition is observed among populations of sub-Saharan African, Hispanic, South Asian, and West Indian descent.[16]

MIS-C is characterized by an excessive immune response resulting in activation of T cells and macrophages with the release of pro-inflammatory cytokines, such as interleukin 6, 8, and 18 (IL-6, IL-8, IL-18), tumor necrosis factor alpha (TNF- α), and interferon γ (IFN-γ).[2,10] Genetic susceptibility to MIS-C is linked to mutations in immune response genes.[23] The characteristics of MIS-C is similar to Kawasaki disease (KD), toxic shock syndrome or macrophage activation syndrome (MAS).[18,24] The hemophagocytic syndrome associated with MIS-C can be attributed to MAS. It was proven to be one of the most important factors determining the severity of the course of MIS-C. The frequency

Table 2. Biological Tests in Our Study.

Biological tests	Normal values	Numbers of patients (N = 52)	Percentage (%)
Hyperleukocytosis (>10 000/mm³)	4000-10 000/mm³	32	62
Neutrophilia (>8000/mm³)	1500-7500/mm³	20	38
Lymphopenia (<1500/mm³)	1500-7500/mm³	24	46
Thrombocytosis (>400 000/mm³)	150 000-400 000/mm³	20	38
Thrombocytopenia (<150 000/mm³)	150 000-400 000/mm³	9	17
CRP > 100 mg/l	<6 mg/l	52	100
ESR > 40 mm/h	2-34 mm/h	30	58
PCT > 2 ng/ml	<2 ng/ml	11	21
Hyperferritinemia (>500 ng/ml)	13.7-78.8 ng/ml	21	40
D-Dimer (>500 ng/ml)	<500 ng/ml	30	58
Hyperfibrinogenemia (>4 g/l)	1.9-4 g/l	26	50
Troponin (>12 ng/l)	<12 ng/l	21	40
Pro-BNP (>1000 pg/ml)	<300 pg/ml	25	48
Hepatic cytolysis			
ASAT (>50 UI/l)	15-50 UI/l	11	21
ALAT (>45 UI/l)	5-45 UI/l	10	19
Renal insufficiency			
Creatinine (>10 mg/l)	2.2-5.9 mg/l	3	6
Urea (>1 g/l)	0.10-0.55 g/l	4	8
Hyponatremia < 130 mmol/l	135-143 mmol/l	11	21
Hypoalbuminemia < 30 g/dl	37-50 g/dl	6	12
Hypoproteinemia < 60 g/l	60-80 g/l	6	12
LDH > 300 UI/l	<300 UI/l	6	12
Triglyceride > 1,5 g/l	<1.5 g/l	6	12

Table 3. Radiological Exams in Our Study.

Radiological exams	Patients numbers (Total = 52)	Percentage (%)
Thoracic scan		
Bilateral pleuropneumopathy	7	13
Ground glass opacities	5	10
Pneumothorax	1	2
Pneumomediastinum	1	2
Echocardiography		
Myocarditis	6	12
Pericarditis	4	8
Coronary artery dilatation (>3 mm)	4	8
Coronary artery aneurysm	1	2

of cytokine storm syndrome in MIS-C and active COVID-19 depended on the scoring systems applied to identify MAS and hemophagocytic lymphohistiocytosis (HLH).[25-27]

Specific diagnostic criteria of MIS-C were initially proposed by the Royal College of Pediatrics and Child Health (RCPCH)[16] (Table 5) and later adapted by the WHO (Table 6)[3] and the Centers for Disease Control and Prevention (CDC)[14] (Table 7). MIS-C can affect all pediatric age groups.[8,10,12] However, the most children with Kawasaki disease presented symptoms before the age of 5 years.[28,29] KD is a rare acute pediatric vasculitis. It is relatively uncommon, with an incidence rate of 20.8 per 100 000 in the United States. It usually involves small to medium sized arteries in various organs and tissues and can cause coronary artery aneurysm, myocardial infarction, and pericarditis. It is characterized by fever, exanthema, lymphadenopathy, conjunctival injection,

Table 4. Characteristics of Multisystem Inflammatory Syndrome in Children Associated With COVID-19.

Study	Patients	Median age (IQR)	Clinical signs (%)	Positive PCR/Serology COVID-19 (%)	Echocardiography (%)	Death (%)
Pouletty et al[8] (France)	16 8 F 8 M	10 years (4.7-12.5)	-Cutaneous: 81 -Gastrointestinal: 81 -Shock: 69 -Neurological: 56 -Respiratory: 12	-PCR: 69 -Serology: 43	-Myocarditis: 44 -Pericarditis: 25 -Dilation of coronary arteries: 19	0
Riphagen et al[17] (United Kingdom)	8 3 F 5 M	8.8 years (6-14)	-Cutaneous: 62.5 -Gastrointestinal: 87.5 - Shock: 87.5 - Neurological: 25 - Respiratory: 25	-PCR: 100 -Serology: 100	- Dilation of coronary arteries: 25 -Left ventricular dysfunction: 25 -Left ventricular dilatation: 12,5	-
Verdoni et al[10] (Italy)	10 3 F 7 M	7.5 years	-Cutaneous: 80 -Gastrointestinal: 60 - Shock: 20 - Neurological: 40	-PCR: 20 -Serology: 80	- Pericarditis: 40 -Mitral insufficiency: 40 -Coronary artery aneurysm: 20	0
Feldstein et al[12] (USA)	186 71 F 115 M	8,3 years (3.3-12.5)	-Cutaneous: 74 -Gastrointestinal: 92 - Shock: 48 - Respiratory: 70	-PCR: 39 -Serology: 15	-Coronary artery aneurysm: 8	0
Akca et al[18] (Turkey)	4 3 F 1 M	5,25 years (2-14)	- Cutaneous: 100 -Gastrointestinal: 25 - Shock: 25 - Respiratory: 25	-PCR: 25 -Serology: 25	- Dilation of coronary arteries: 25	25
Abrams et al[19] (USA)	1080 478 F 602 M	8 years (4-12)	- Cutaneous: 29 -Gastrointestinal: 64 - Shock: 36 - Respiratory: 30	-	- Myocarditis: 18 -Dilation of coronary arteries: 17	2
Acevedo et al[20] (Colombia)	78 32 F 46 M	7 years (1-11)	- Cutaneous: 44 -Gastrointestinal: 74 - Shock: 78 - Respiratory: 29 -Acute kidney injury: 29	-PCR: 68 - Serology: 24	- Pericardial effusion: 36 -Dilation of coronary arteries or aneurysm: 35 - Mitral regurgitation: 21 - Aortic regurgitation: 2.5	9
Sacco et al[21] (Chile)	76 35 F 41 M	8 years (3-11)	- Cutaneous: 62 -Gastrointestinal: 86 - Shock: 47 - Respiratory: 36 - Neurological: 39	-PCR: 21 -Serology: 100	-Coronary artery involvement: 8	-
Grama et al[22] (Roumania)	34 13 F 21 M	6,8 years (±4,6 years)	- Cutaneous: 64,71 -Gastrointestinal: 79,41 - Shock: 11,76 - Respiratory: 38,24 - Neurological: 70,59 -Acute kidney injury: 20,59	-Serology: 100	-Decreased left ventricular ejection fraction: 20,58 - Pericardial effusion: 26,47	0
Our study (Morocco)	52 24 F 28 M	6 years (1-14)	- Cutaneous: 80 -Gastrointestinal: 44 - Shock: 17 - Neurological: 8 - Respiratory: 58 -Acute kidney injury: 4	-PCR: 19 -Serology: 81	- Myocarditis: 12 - Pericarditis: 8 -Dilation of coronary arteries: 8 -Coronary artery aneurysm: 2	0

Abbreviations: F, female; M, male; PCR, polymerase chain reaction.

Table 5. Diagnosis Criteria of MIS-C by the Royal College of Pediatrics and Child Health (RCPCH).[16]

1. All children (age not defined),
2. Persistent fever ≥38.5°C,
3. Single or multiorgan dysfunction and additional features abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucous membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope, vomiting,
4. Neutrophilia, elevated CRP and lymphopenia,
5. Exclusion of other infections, including bacterial sepsis, staphylococcal or streptococcal shock syndromes,
6. SARS-CoV-2 PCR test may be positive or negative.

Table 6. Diagnosis Criteria of MIS-C by the World Health Organization.[3]

1. Age from 0 to 19 years,
2. Fever for ≥3 days,
3. Clinical signs of multisystem lesion (at least 2 of the following):
   - Rash, bilateral non-purulent conjunctivitis, or signs of inflammation of the skin and mucous membranes (oral, hands, or feet);
   - Hypotension or shock;
   - Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic data or elevated troponin/BNP);
   - Signs of coagulopathy (prolonged PT or PTT; elevated D-dimer).
   - Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4. Elevated inflammatory biomarkers (ESR, CRP, or procalcitonin),
5. The absence of an obvious microbial cause of multisystem inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndrome,
6. Signs of previous COVID-19: Any of the following: Positive PCR of SARS-CoV-2/Positive serological studies/Positive antigen test/Contact with a person with confirmed COVID-19.

Table 7. Diagnosis Criteria of MIS-C by the Center for Disease Control and Prevention.[14]

1. Age < 21 years, fever ≥ 38°C for ≥24 hours, or subjective fever lasting ≥ 24 hours,
2. Laboratory evidence of inflammation,
3. Multisystem organ involvement (≥2) requiring hospitalization: cardiac, renal, respiratory, hematological, gastrointestinal, dermatologic, or neurological,
4. At least one of the following: elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, IL-6, neutrophilia, lymphopenia, Hypoalbuminemia,
5. Positive for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test, or COVID-19 exposure within the 4 weeks prior to symptom onset,
6. No alternative diagnosis.

and changes to the mucosa and extremities.[30] MAS is accompanied primarily by manifestations of serious hematological, hepatic, and neurological dysfunction with the need for intensive therapeutic measures.[25-27] The main clinical signs of MIS-C (Table 4) include prolonged fever, rash, cheilitis, non-purulent conjunctivitis, cervical lymphadenopathy, cardiac dysfunction associated with respiratory, gastrointestinal, and neurological signs.[8,16] Pouletty et al.[8] noted cutaneous and gastro-intestinal signs in (81%) of cases, shock in (69%), neurological signs in (56%), and respiratory manifestations in (12%). However, Acevedo et al.[20] detected acute kidney injury (29%), cutaneous signs (44%), shock (78%), and respiratory manifestations (29%). This clinical presentation is close to the manifestations reported in our study. Pericarditis and/or myocarditis are common in MIS-C. However, coronary involvement is rare and transient when compared with KD.[8,29] Shock is quite common in MIS-C. In the various series published, half of the cases required vasoactive drugs.[6,11] Valverde et al.[31] detected a high incidence of myocardial involvement in (93%) of cases, shock in (40%), and arrythmia (35%). However, we noted myocarditis in (12%) of cases, shock in (17%), and pericarditis (8%).

In most cases described, serological tests were positive, but only a small percentage of children had a positive PCR result on a nasopharyngeal swab.[32] MIS-C appears to be a delayed post-infectious immunological phenomenon rather than directly related to acute, symptomatic, or asymptomatic early infection with SARS-CoV-2.[11,12,33] Serological tests have some advantages over PCR such as the presence of antibodies in the blood over a long period, unlike viral RNA.[18] Confirmation of SARS-CoV-2 infection is not proven by serology, PCR, or positive antigen detection; having a contact with COVID-19 within 4 weeks preceding diagnosis is considered sufficient.[6,18] Feldstein et al.[12] indicated that 70% of patients had positive PCR or antibody testing and 30% had exposure to a person with COVID-19 within the last 4 weeks (Table 4).

MIS-C is characterized by a major inflammatory syndrome with a significant elevation of inflammatory markers: CRP, PCT, ESR, Ferritinemia.[6,14,34] Interleukin 6 levels correlate with clinical severity of MIS-C.[35] Hyperleukocytosis with neutrophilic polynucleosis, lymphopenia and thrombocytosis are common during this syndrome. Coagulation abnormalities are also present, such as hyperfibrinogenemia and elevated D-dimer levels (>5 times normal).[6,8,14,34] Hyponatremia, hypoalbuminemia, and hepatic cytolysis were also found in the literature.[6,14,34,36,37] Some of investigations are necessary to diagnose a life-threatening complication, such as the search for renal insufficiency (creatinine, urea) and myocarditis by measuring troponin and NT-Pro-BNP.[8] Minocha et al.[38] showed that the majority of patients (78%) had at least one abnormality in cardiac testing, including abnormal echocardiography in (30%), elevated pro-BNP in (43%), and/or elevated Troponin in (21%). Troponin levels are usually moderately elevated.[17] However, NT-Pro-BNP or BNP levels are very high in severe forms, up to 20,000 pg/ml compared with a norm of less than 400 pg/ml. NT-Pro-BNP or BNP measurement should, therefore, be part of the initial biological assessment when MIS-C is suspected.[6] In an English study of 58 cases,[34] the presence of shock was correlated with elevated inflammatory and cardiac markers (NT-Pro-BNP and Troponin).[6] Patients with biological markers of heart failure (BNP > 1000 pg/ml) or significant inflammation (CRP > 200 mg/l) should be transferred immediately to an intensive care unit.[6,34] Acute kidney injury occurs in 25% to 33% of MIS-C patients. The mechanism of acute kidney injury in COVID-19 patients is multifactorial and includes dehydration, low cardiac output, cytokine storm, the direct cytopathic effect of the virus on renal tubular cells, and the use of nephrotoxic drugs. However, the mechanism involved in the development of acute kidney injury in MIS-C patients is mainly due to renal hypoperfusion.[39]

The therapeutic management of MIS-C has a specific feature. The combination of intravenous immunoglobulin and high dose of intravenous corticosteroids has shown superiority to immunoglobulin alone, with faster recovery of cardiac function.[6,40] Corticosteroids boluses may be considered in cases of severe progression or when risk factors are present.[8] In case of unfavorable evolution with the combination of immunoglobulins and corticosteroids, anti-IL-6 (Tocilizumab) or anti-IL-1 (Anakinra) biotherapy should be considered. Biotherapy aims to limit cytokine shock.[8,41-43] In our series, we didn't used the biotherapy due to high cost. Antibiotic therapy with intravenous C3G is recommended for the first 48 hours, until a bacteriological cause of the fever has been ruled out.[6,8] In the event of shock, vasopressor/inotropic drugs or ventilation should be initiated rapidly.[6] Hemostasis abnormalities and/or the existence of thromboembolic risk factor should lead to anticoagulation, in the absence of contraindication, with low-dose subcutaneous low-molecular-weight heparin (LMWH). In the case of renal insufficiency, unfractionated heparin is used as a continuous intravenous drip.[44] Aspirin at an anti-platelet aggregation dose (3-5 mg/kg/day) is started and continued for 8 weeks (maximum 100 mg/day). Aspirin may be initiated immediately if there is no indication for anticoagulant thromboprophylaxis.[6,45]

Regarding short-term evolution, the combination of intravenous immunoglobulins and corticosteroids leads to rapid clinical improvement within the first 48 hours. Indeed, it is effective in over 90% of cases.[6,40] Patients on vasopressor or vasoactive therapy can be weaned rapidly. The inflammatory assessment also improves within a few days, then usually normalizes.[6,45] Normalization of systolic function occurs within 4 days, when systolic function is impaired on admission, and within 7 days for diastolic function.[6,40] Coronary aneurysms can develop during the convalescent phase of the illness, consequently, echocardiographic follow-up is important, even for patients who did not show cardiac involvement during the acute phase.[4] Overall mortality from MIS-C is low[12,34] (Table 4). Early diagnosis and the combination of corticosteroid therapy and immunoglobulins allowed avoiding death in our series. Finally, the limitations of our study are related to the retrospective monocentric study design, missing data, relatively small sample size and the impossibility of having the laboratory data from the same time point. We fully understand that these limitations can affect the study results. Prospective studies are needed to compare the different strategies of early recognition, availability of resources and type of treatments used to better understand the differences found and the MIS-C outcomes in countries with limited resources compared to high-income countries.

Conclusion

Multisystem inflammatory syndrome in children associated with COVID-19 infection is a novel pediatric syndrome. It characterized by elevated inflammatory markers and multi-organ involvement. We identified myocarditis as the predominant cardiac involvement, although we also observed rare cases of acute kidney injury. The combination of intravenous immunoglobulin and corticosteroids has shown superiority to immunoglobulin alone, with faster recovery of cardiac function in this study. Despite a high level of morbidity, the majority of patients experience have a good outcome, with no fatalities reported.

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Author Contributions

Pr. Naima Amenzoui: Pediatric professor (collecting, analyzing the data, and redaction of the original article). **Dr. Siham Zouiter**: Pediatric resident (collecting, analyzing the data, and redaction of the original article). **Dr. Meriem Nassid**: Pediatrician (collecting and analyzing the data in our series). **Dr. Halima Kholaiq**: Phd Doctor (collecting and analyzing the data in our series). **Dr. Ikbal Belkhou**: Pediatrician (collecting and analyzing the data in our series). **Pr. Ibtihal Benhsaien**: Pediatric professor (collecting and analyzing the data in our series). **Pr. Fatima Ailal**: Pediatric professor (collecting and analyzing the data in our series). **Pr. Fatima Adnane**: Pediatric professor (collecting and analyzing the data in our series). **Pr. Zineb Jouhadi**: Pediatric professor (collecting and analyzing the data in our series). **Pr. Ahmed Aziz Bousfiha**: Pediatric professor (collecting and analyzing the data in our series).

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

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