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Clinical Characteristics, Treatment, and Outcomes of Multisystem Inflammatory Syndrome in Children Associated with COVID-19: A Single-Center Study from Iran

Hossein Masoumi-Asl [1], Zahra Vahedi [1], Sedigheh Yousefzadegan [1], Ashraf Mousavi [1], Ramin Zare-Mahmoudabadi [1], Mohamad Vafaee Shahi [2], Kourosh Kabir [3,1], Hirad Houjaghani [4], Reza Behmadi [1], Soheila Mahdavynia [1,*]

[1] Firoozabadi Clinical Research Development Unit (FACRDU), Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2] Growth and Development Research Center, Institute of Endocrinology and Metabolism, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[3] Department of Community and Family Medicine, Preventive Medicine and Public Health Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[4] Faculty of Medicine, Iran University of Medical Sciences (IUMS), Tehran, Iran

[*] ***Corresponding Author:*** Firoozabadi Clinical Research Development Unit (FACRDU), Department of Pediatrics, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. Email: dr.so.mahdavynia@hotmail.com

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Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious post-infectious inflammatory condition associated with SARS-CoV-2 infection in children. While the pathogenesis remains unclear, it is considered an immune-mediated hyper inflammatory reaction triggered by the virus.

Objectives: To investigate the clinical characteristics, laboratory findings, treatments, and outcomes of MIS-C cases in an Iranian hospital.

Methods: A retrospective review was conducted of 102 children meeting the World Health Organization (WHO) diagnostic criteria for MIS-C admitted to Firoozabadi Hospital in Tehran from March 2020 to February 2021. Demographic, clinical, laboratory, and outcome data were extracted from medical records.

Results: Fever (96.1%) and cough (47.1%) were the most common presenting symptoms, followed by ill appearance (47.1%), nausea/vomiting (36.3%), and dyspnea (35.3%). Neurological involvement included seizures in 28.4% of cases. Lymphopenia was observed in 55.5% of patients, and abnormal blood gas levels, including hypocapnia or hypercapnia, were present in 90.6% of cases. Common treatments included antibiotics (78.0%), corticosteroids (44.0%), remdesivir (25.0%), and IVIG (13.0%). The recovery rate was 90.2%, with 26.5% of patients requiring PICU admission, and a mortality rate of 9.8%.

Conclusions: This study provides epidemiological data on MIS-C in Iran, demonstrating both similarities and differences compared to previous literature. The high rate of respiratory and neurological involvement, along with distinct treatment patterns, highlights the need for further research to optimize management strategies across different healthcare settings.

Keywords: Multisystem Inflammatory Syndrome in Children (MIS-C), COVID-19, Pediatrics

1. Background

The emergence of the novel SARS-CoV-2 virus responsible for the COVID-19 outbreak has challenged global healthcare systems, leading to widespread morbidity and mortality (1). A concerning development has been the identification of multisystem inflammatory syndrome in children (MIS-C), a rare but serious hyperinflammatory condition associated with SARS-CoV-2 infection in children (2, 3). The MIS-C involves inflammation affecting multiple organ systems, including the heart, lungs, kidneys, brain, skin,

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eyes, and gastrointestinal system (4). The MIS-C occurs predominantly in those with current or recent COVID-19 infection, even in mild or asymptomatic cases. The MIS-C often initially presents similarly to Kawasaki disease or toxic shock syndrome but can rapidly progress to a life-threatening illness with cardiovascular shock and multiorgan failure (5).

The exact pathogenesis of MIS-C remains unclear, but current insights suggest an immune-mediated hyperinflammatory response to SARS-CoV-2 infection in children (6, 7). Viral molecular patterns could trigger a "cytokine storm", resulting in systemic inflammation and multiorgan dysfunction as seen in MIS-C (8, 9). Genetic factors play a role in determining individual susceptibility to MIS-C following SARS-CoV-2 exposure. Not all exposed children develop MIS-C, suggesting underlying genetic variations contribute to differential responses (10).

Diagnostic criteria for MIS-C include: (1) Muco-cutaneous inflammation signs; (2) shock or hypotension; (3) evidence of cardiac dysfunction or coronary anomalies; (4) elevated troponin or natriuretic peptide levels; (5) coagulopathy; and (6) gastrointestinal symptoms, according to World Health Organization (WHO) diagnostic criteria for MIS-C (11). Differential diagnoses include sepsis, toxic shock syndromes, macrophage activation syndrome, and hemorrhagic fevers. As MIS-C has an unknown pathophysiology, a COVID-19 test is useful but not required for diagnosis. The presence of multiorgan dysfunction and hyperinflammation in the appropriate context is most indicative of MIS-C. Rapid recognition and management are critical given the potential morbidity and mortality.

2. Objectives

The present study aims to characterize the clinical features, laboratory findings, treatment approaches, and outcomes of MIS-C in an Iranian tertiary care center, contributing to the growing understanding of this condition's manifestations across different populations and healthcare settings.

3. Methods

3.1. Study Design and Setting

This retrospective observational study was conducted at Firoozabadi Hospital, a tertiary care center in Tehran, Iran. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (approval number: IR.IUMS.REC.1400.609, dated 28/09/2021).

3.2. Sample Size Calculation

The sample size was calculated using the formula for estimating a proportion with specified precision:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}}\, p\left(1-p\right)}{d^2} \quad (1)$$

Where $Z_{1-\frac{\alpha}{2}} = 1.96$ for a 95% confidence level, P is the expected proportion of MIS-C (based on previous studies), and d is the margin of error.

3.3. Participants

During the study period (March 2020 to February 2021), 102 patients diagnosed with MIS-C were included. The inclusion criteria followed WHO diagnostic criteria for MIS-C: (1) Age 0 - 19 years; (2) fever for ≥ 3 days; (3) two or more of the following: Rash, conjunctivitis, mucocutaneous inflammation signs, hypotension/shock, cardiac involvement, coagulopathy, acute gastrointestinal problems; (4) elevated markers of inflammation; (5) no other obvious microbial cause; and (6) evidence of COVID-19 or likely contact with patients. Patients were excluded if they had negative RT-PCR, serology, and chest CT for COVID-19.

3.4. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 26.0 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables are presented as frequencies and percentages, n (%). Continuous variables are expressed as mean ± standard deviation or median (interquartile range) based on distribution normality. Chi-square or Fisher's exact tests were used for comparing categorical variables between groups. Post-hoc power analysis was performed to validate the adequacy of sample sizes for subgroup comparisons. A P-value < 0.05 was considered statistically significant.

4. Results

4.1. Demographic Characteristics

Among the 102 patients diagnosed with MIS-C, 58 (56.9%) were male and 44 (43.1%) were female. The age distribution showed 41 (40.2%) patients under 1 year, 21

Table 1. Demographic Characteristics of Children with Multisystem Inflammatory Syndrome in Children (N = 102) [a]

Variables	Values
Sex [b]	
Male	58 (56.9)
Female	44 (43.1)
Age groups (y) [c]	
< 1	41 (40.2)
1 - 2.99	21 (20.6)
3 - 5.99	14 (13.7)
6 - 8.99	8 (7.8)
9 - 11.99	10 (9.8)
≥ 12	8 (7.8)
Area of residence [d]	
Urban	90 (88.2)
Rural	12 (11.8)
Nationality [e]	
Iranian	80 (78.4)
Non-Iranian	22 (21.6)

[a] Values are expressed as No. (%).

[b] Chi-square test used for sex distribution.

[c] Age groups defined with non-overlapping intervals.

[d] Fisher's exact test used for residence comparison.

[e] Chi-square test used for nationality comparison.

Table 2. Clinical Signs and Symptoms in Children with Multisystem Inflammatory Syndrome in Children (N = 102) [a]

Clinical Features	No. (%)	95% CI
Fever	98 (96.1)	92.4 - 99.8
Cough	48 (47.1)	37.7 - 56.7
Ill appearance	48 (47.1)	37.7 - 56.7
Nausea/vomiting	37 (36.3)	27.6 - 45.9
Dyspnea	36 (35.3)	26.7 - 44.9
Seizure	29 (28.4)	20.6 - 37.8
Diarrhea	26 (25.5)	18.0 - 34.7
Loss of appetite	18 (17.6)	11.5 - 26.2
Rhinorrhea	17 (16.7)	10.7 - 25.1
Pneumonia	16 (15.7)	9.9 - 24.0
Chest wall retraction	14 (13.7)	8.4 - 21.7
RDS	13 (12.7)	7.6 - 20.6
LOC	13 (12.7)	7.6 - 20.6

Abbreviations: RDS, respiratory distress syndrome; LOC, loss of consciousness.

[a] Chi-square test used for comparison of proportions.

(20.6%) between 1 - 2.99 years, 14 (13.7%) between 3 - 5.99 years, 8 (7.8%) between 6 - 8.99 years, 10 (9.8%) between 9 - 11.99 years, and 8 (7.8%) were ≥ 12 years. Urban residents comprised 90 (88.2%) of cases, while 80 (78.4%) were Iranian nationals (Table 1).

4.2. Clinical Presentation

The most frequent clinical manifestations (Table 2) included fever in 98 (96.1%) patients, cough in 48 (47.1%), and ill appearance in 48 (47.1%). Respiratory symptoms

Table 3. Laboratory and Imaging Findings in Children with Multisystem Inflammatory Syndrome in Children

Parameters	Total Assessed (N)	Abnormal Results; No. (%)	95% CI
Hematologic parameters			
Lymphopenia (< 1500/μL)	101	56 (55.4)	45.8 - 65.1
Leukocytosis (> 12000/μL)	102	33 (32.4)	23.3 - 41.4
Leukopenia (< 4000/μL)	102	15 (14.7)	7.8 - 21.6
Thrombocytopenia/thrombocytosis [a]	102	30 (29.4)	20.6 - 38.3
Anemia (Hb < 10 g/dL)	102	17 (16.7)	9.4 - 23.9
Inflammatory markers			
Elevated LDH (> 400 U/L)	62	51 (82.3)	72.8 - 91.8
Elevated CRP (> 5 mg/dL)	96	22 (22.9)	14.5 - 31.3
Elevated ESR (> 15 mm/h)	69	24 (34.8)	23.5 - 46.0
D-dimer (> 400 mg/L FEU)	67	18 (26.9)	16.3 - 37.5
Blood chemistry			
Elevated BUN (> 20 mg/dL)	100	90 (90.0)	84.1 - 95.9
Abnormal sodium [b]	101	75 (74.3)	65.7 - 82.8
Abnormal potassium [c]	101	16 (15.8)	8.7 - 23.0
Elevated creatinine (> 1 mg/dL)	99	7 (7.1)	2.0 - 12.1
Blood gas analysis			
Abnormal PCO_2 [d]	96	87 (90.6)	84.8 - 96.5
Abnormal HCO_3 [e]	95	70 (73.7)	64.8 - 82.5
Abnormal pH [f]	96	63 (65.6)	56.0 - 75.2
Imaging			
Abnormal echocardiogram	47	25 (53.2)	38.9 - 67.5
COVID-19 positive HRCT	102	19 (18.6)	11.1 - 26.2

[a] < 150,000 or > 450,000/μL.
[b] < 135 or > 145 mEq/L.
[c] < 3.5 or > 5.5 mEq/L.
[d] < 40 or > 44 mmHg.
[e] < 20 or > 24 mEq/L.
[f] < 7.35 or > 7.45.

were prominent, with dyspnea in 36 (35.3%) cases and chest wall retraction in 14 (13.7%). Gastrointestinal manifestations included nausea/vomiting in 37 (36.3%) and diarrhea in 26 (25.5%). Notably, neurological involvement was significant, with seizures occurring in 29 (28.4%) patients and loss of consciousness in 13 (12.7%). Respiratory distress syndrome (RDS) developed in 13 (12.7%) cases.

4.3. Laboratory and Imaging Findings

Laboratory findings (Table 3) revealed significant hematological abnormalities, with lymphopenia (< 1500 cells/μL) in 56/101 (55.45%) patients. Complete data was available for most parameters, though some tests had missing values: D-dimer (67/102), albumin (39/102), and cardiac markers (47/102). Blood gas analysis showed acid-base disturbances in the majority of cases, with abnormal PCO_2 (< 40 or > 44 mmHg) in 87/96 (90.63%) and abnormal bicarbonate in 70/95 (73.68%) patients. Inflammatory markers were frequently elevated, with high LDH (> 400 units/L) in 51/62 (82.26%) and elevated BUN in 90/100 (90.0%) cases.

Cardiac evaluation by echocardiography, performed in 47 patients, showed abnormalities in 25 (53.19%) cases. SARS-CoV-2 PCR was positive in 81 (79.41%) patients, while chest HRCT showed ground glass opacities consistent with COVID-19 in 19 (18.63%) cases.

4.4. Treatment Approaches

Treatment strategies (Table 4) varied, with antibiotics being the most commonly administered therapy in 78 (78.0%) patients. Immunomodulatory therapy included

Table 4. Treatment Modalities Used in Children with Multisystem Inflammatory Syndrome in Children (N = 102) [a, b]

Treatments	Values
Antibiotics	78 (78.0)
Corticosteroids	44 (44.0)
Remdesivir	25 (25.0)
IVIG	13 (13.0)
Kaletra [c]	3 (3.0)

[a] Values are expressed as No. (%).

[b] Chi-square test used for comparison of treatment frequencies.

[c] Lopinavir/ritonavir.

Table 5. Clinical Outcomes in Children with Multisystem Inflammatory Syndrome in Children (N = 102) [a]

Variables	No. (%)	95% CI
Recovery	92 (90.2)	84.4 - 96.0
PICU admission	27 (26.5)	17.9 - 35.0
Intubation	11 (10.8)	4.9 - 17.1
Mortality	10 (9.8)	4.0 - 15.6

[a] Chi-square test used for outcome comparisons.

corticosteroids in 44 (44.0%) and IVIG in 13 (13.0%) cases. Antiviral therapy with remdesivir was used in 25 (25.0%) patients. Kaletra (lopinavir/ritonavir) was administered in 3 (3.0%) cases, specifically in patients with severe respiratory symptoms and early in the pandemic before treatment protocols were established.

4.5. Clinical Outcomes

Overall, 92 (90.2%) patients recovered, while 10 (9.8%) died (Table 5). PICU admission was required for 27 (26.47%) patients, and 11 (10.80%) needed mechanical ventilation. Analysis of mortality risk factors (Table 6) showed significantly higher rates among non-Iranian nationals (7/22, 31.8%) compared to Iranian patients (3/80, 3.8%) ($P < 0.001$). Mortality was also significantly higher in patients who developed RDS (5/13, 38.5% vs 5/89, 5.6%, $P < 0.001$) and those requiring intubation (6/11, 54.5% vs 4/91, 4.4%, $P < 0.001$).

5. Discussion

This study provides important insights into the characteristics and clinical features of MIS-C in an Iranian hospital setting, revealing both similarities and differences compared to previously reported cohorts. Our findings contribute to the growing understanding of how this syndrome manifests across different populations and healthcare environments. Our cohort showed a slight male predominance (56.9%), consistent with previous studies. However, the age distribution in our population differed notably from other reports, with 40.2% of cases occurring in children under one year. This contrasts with most published series where the median age is typically 8 - 9 years (12, 13). This difference could reflect variations in local testing practices, referral patterns, or potentially distinct disease manifestations in our population, warranting further investigation.

The clinical presentation in our cohort demonstrated some unique features. While fever was present in 96.1% of cases, aligning with standard diagnostic criteria, we observed higher rates of respiratory symptoms (47.1% with cough) compared to previous reports (14, 15). The high prevalence of gastrointestinal symptoms (36.3% with nausea/vomiting, 25.5% with diarrhea) aligns with the growing recognition of significant GI involvement in MIS-C (16, 17). A striking finding was the high rate of neurological manifestations, with seizures occurring in 28.4% of patients, substantially higher than typically reported (18). This observation highlights the need for careful neurological monitoring in MIS-C patients and suggests potential regional variations in disease presentation or severity.

Table 6. Mortality Rates by Demographics and Clinical Variables

Variables	Total (N)	Mortality; No. (%)	P-Value [a]
Sex			0.742
Male	58	5 (8.6)	
Female	44	5 (11.4)	
Age			0.084
< 1	41	7 (17.1)	
1 - 3	21	0 (0.0)	
3 - 6	14	0 (0.0)	
6 - 9	8	0 (0.0)	
9 - 12	10	1 (10.0)	
> 12	8	2 (25.0)	
Nationality			< 0.001 [b]
Iranian	80	3 (3.8)	
Non-Iranian	22	7 (31.8)	
Residence			0.334
Urban	90	8 (8.9)	
Rural	12	2 (16.7)	
RDS			< 0.001 [b]
Yes	13	5 (38.5)	
No	89	5 (5.6)	
Intubation			< 0.001 [b]
Yes	11	6 (54.5)	
No	91	4 (4.4)	

Abbreviation: RDS, respiratory distress syndrome.

[a] Chi-square test unless otherwise specified.

[b] Fisher's exact test.

Laboratory findings showed patterns of immune dysregulation consistent with MIS-C, including lymphopenia in 55.45% of cases (19). The remarkably high rate of blood gas abnormalities (90.63% with abnormal PCO_2) suggests significant metabolic derangement, possibly reflecting the severity of systemic inflammation or cardiorespiratory involvement. These findings emphasize the importance of close monitoring of acid-base status in MIS-C patients. The cardiac involvement rate (53.19% with abnormal echocardiography) aligns with previous studies (20, 21)and reinforces the need for cardiac evaluation in all suspected cases. The high PCR positivity rate (79.41%) in our cohort is notable and may reflect differences in the timing of presentation or testing strategies compared to other centers (22).

Our treatment approaches showed some variation from international practices, reflecting the evolving nature of MIS-C management and potential resource considerations. The relatively low use of IVIG (13%) compared to other centers likely reflects a combination of factors including resource availability, cost constraints, and evolving treatment protocols during the study period (23). The higher use of antibiotics (78%) may represent a more conservative approach given the challenge of differentiating MIS-C from severe bacterial infections early in the disease course.

The overall recovery rate of 90.2% is encouraging, though our mortality rate (9.8%) is higher than reported in many series (24, 25). This difference might reflect several factors, including: (1) The high proportion of young infants in our cohort; (2) variations in healthcare access and resources; (3) potential differences in disease severity or presentation.

The significantly higher mortality among non-Iranian nationals ($P < 0.001$) raises important questions about healthcare access and potential socioeconomic disparities that warrant further investigation. Similarly, the strong association between mortality and respiratory complications (RDS and intubation, P <

0.001) highlights the critical importance of respiratory support in severe cases.

5.1. Conclusions

This study provides valuable insights into the manifestations and outcomes of MIS-C in an Iranian healthcare setting. The distinct patterns observed in our cohort, including younger age at presentation, high rates of neurological involvement, and variation in treatment approaches, highlight the importance of understanding regional differences in MIS-C presentation and management. These findings can help inform clinical practice and future research directions, particularly in similar healthcare settings.

5.2. Future Research

Our findings suggest several important areas for future research: (1) Prospective studies to better understand age-related variations in MIS-C presentation and outcomes; (2) investigation of factors contributing to the high rate of neurological complications in our population; (3) evaluation of optimal treatment strategies in resource-limited settings; (4) assessment of socioeconomic factors affecting MIS-C outcomes; (5) long-term follow-up studies to understand the chronic sequelae of MIS-C.

5.3. Limitations

Several limitations should be considered when interpreting our findings: (1) As a single-center retrospective study, our results may not be generalizable to other populations or healthcare settings; (2) missing data for some laboratory parameters might affect the comprehensiveness of our analyses; (3) the high proportion of infants in our cohort may influence the overall clinical picture and outcomes; (4) treatment protocols evolved during the study period as understanding of MIS-C improved; (5) long-term follow-up data were not available.

Footnotes

Authors' Contribution: Study concept and design: H. M. A.; Acquisition of data: S. Y., A. M., R. Z. M., M. V. S., and R. B.; Analysis and interpretation of data: K. K.; Drafting of the manuscript: Z. V. and H. H.; Critical revision of the manuscript for important intellectual content: H. M. A.; Statistical analysis: K. K.; Administrative, technical, and material support: S. M.; Study supervision: H. M. A. and S. M.

Conflict of Interests Statement: The authors declare no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: The authors declare the study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1400.609).

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