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Clinical features and outcome of multisystem inflammatory syndrome in children (MIS-C) patients in northwest general hospital and research center Peshawar

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ABSTRACT

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) is a post–COVID-19 hyperinflammatory condition with multisystem involvement. Due to limited regional data, this study assessed the clinical features and outcomes of MIS-C in children admitted to Northwest General Hospital, Peshawar.

Methods: A six-month descriptive cross-sectional study was conducted after ethical approval. Seventy-nine patients aged 0–19 years meeting WHO/CDC MIS-C criteria were included through sequential sampling. Clinical presentation, laboratory findings, treatment, and outcomes were recorded and analyzed using SPSS 23. Results were reported as frequencies, percentages, and means where appropriate.

Results: Most patients were 6–12 years old (44.3%) and female (63.3%). Prior COVID-19 exposure was documented in 69.6%, and 72.2% had elevated antibody titers. Common symptoms were reduced oral intake (59.5%), rash (45.6%), conjunctival congestion (40.5%), vomiting (40.5%), abdominal pain (29.1%), hypotension (35.4%), and tachycardia (32.9%). CRP (74.7%), ESR (49.4%), and AST (51.9%) were the most frequently elevated markers. Cardiac dysfunction occurred in 7.6% of cases. Intravenous immunoglobulins (IVIG, 94.9%) and steroids (72.2%) were the main treatments; 36.7% required inotropes and 3.8% mechanical ventilation. Mortality was 21.5%, significantly higher among those with concurrent measles.

Conclusion: MIS-C commonly involved gastrointestinal, cardiovascular, and mucocutaneous systems. Most children improved with timely Intravenous immunoglobulins, steroid therapy, and supportive care, but coexisting measles was associated with markedly poorer outcomes.

Keywords: Hyperinflammation, Inflammatory Syndrome, SARS-CoV-2

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Introduction

As of March 12, 2022, there have been over 455 million coronavirus disease (COVID-19) cases confirmed globally, resulting in over 6.03 million deaths (1). In adults, COVID-19 caused severe interstitial pneumonia and hyper activation of the inflammatory cascade; however, in children, the illness caused benign respiratory involvement (2). Nevertheless, a number of investigations have shown that children infected with

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience tissue damage mediated by the host innate immunity that is typified by a cytokine storm (3,4). After a child is exposed to the COVID-19 virus for two to six weeks, an inflammatory post viral complication known as multisystem inflammatory syndrome in children (MIS-C) may occur (5). MIS-C associated with SARS-CoV-2, (6), pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIM-TS), (7), and hyper inflammatory shock during the COVID-19 pandemic are some of the terms used to describe this syndrome (8).

Eight kids from the South Thames Retrieval Service in London, UK, provided evidence for the first case series of MIS-C patients (8) who displayed symptoms resembling toxic shock syndrome and Kawasaki disease (KD) (9). Subsequently, reports of comparable cases were received from countries across the globe, including the United States, Italy, France, Israel, and Latin America (2,10). A prior SARS-CoV-2 infection or exposure, along with the exclusion of other possible etiologies, were evidenced by the development of a fever, elevated inflammatory markers, and involvement of at least two systems, according to the case definition for MIS-C created by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) (1). Clinical features of MIS-C and KD are similar, including conjunctival injection, oropharyngeal findings (strawberry tongue and red, cracked lips), rash, swollen, erythematous hands and feet, and cervical lymphadenopathy. In contrast to KD, there was a higher likelihood of shock symptoms, cardiac dysfunction and coronary artery aneurysms on echocardiograms, as well as noticeable neurological and gastrointestinal symptoms in MIS-C patients (2,7,9).

Treatment plans adhere to guidelines; low-dose aspirin is the first line of treatment; sick patients require IVIG, steroids, anticoagulant therapy, and immune modulators such as tocilizumab (4).

Because no local data is available the purpose of the study was to find out diverse clinical presentations and outcomes of children presenting with MISC as it will help us in coming out with our local guidelines on the basis of which future results would be based. Further this will help clinicians to improve their clinical practices and reinforce vaccination for their patients.

Finding out the clinical characteristics and prognosis of patients with multisystem inflammatory syndrome (MIS-C) who were admitted to Northwest General Hospital in Peshawar is the aim of this study.

Methods

This descriptive cross-sectional study was conducted in the pediatric department of Northwest General Hospital and Research Centre (NWGH&RC) after receiving approval from the Institutional Ethical Review Board via letter number IRB &EC - AHL-4421-2022.Duration of study was six months. With a 95% confidence interval, a 5% margin of error, and an expected mortality rate of 5.6% among MIS-C patients, a sample size of 79 was determined using OpenEpi software. All eligible patients who presented throughout the trial period were enrolled until the necessary sample size was obtained using non-probability sequential sampling.

Children and teenagers between the ages of 0 and 19 were classified as having MIS-C if they had a fever that was higher than 99°F for longer than three days, elevated inflammatory markers, such as elevated CRP, procalcitonin, leukocyte count, or platelet

count, and no indication of other microbial causes, such as toxic shock syndromes or bacterial sepsis. Raised COVID-19 antibody titers or a documented history of contact with a confirmed COVID-19 case were used to confirm evidence of earlier SARS-CoV-2 infection. Mucocutaneous indicators like rash and conjunctivitis, gastrointestinal symptoms, hepatic dysfunction, respiratory distress, hypotension, shock, and heart involvement were among the clinical manifestations evaluated.

Troponin-I levels and echocardiography were used in the cardiac evaluation to measure the left ventricular ejection fraction, pericardial effusion, and coronary anomalies. PT, APTT, and D-dimer levels were used to measure coagulopathy. Individuals with proven bacterial or viral infections, pre-existing cardiac or respiratory comorbidities, ongoing COVID-19 infection, or any known inflammatory or autoimmune condition were not included.

All eligible patient's parents or guardians provided informed consent following ethical clearance. A standardized proforma with demographic data, clinical presentation, lab results, and imaging results was used to gather the data. Every patient was monitored during their hospital stay, and results were documented upon discharge. Clinical recovery with stable vital signs, little or absent symptoms, and improvement in inflammatory markers at the time of discharge were considered favorable outcomes. The need for mechanical breathing, inotropic support, more oxygen after discharge, the emergence of cardiorespiratory failure, or death were examples of poor outcomes. To minimize confounders and eliminate bias, strict adherence to the inclusion and exclusion criteria was followed.

SPSS version 23 was used to enter and evaluate all of the data that was gathered. Age, weight, BMI, length of hospital stay, duration of symptoms, and other continuous variables were given as mean ± standard deviation or median and interquartile range based on normality determined by the Shapiro–Wilk test. Frequencies and percentages were used to describe categorical factors, including gender, socioeconomic status, clinical characteristics, laboratory abnormalities, and patient outcomes. Tables and charts were used to display the data. Stratification was used to control for effect modifiers such as age, gender, comorbidities, length of symptoms, and hospital stay. The Chi-square test was used for post-stratification comparisons. Statistical significance was defined as a p-value of less than 0.05.

Results

The cohort consisted of 79 patients, with males forming the majority and females comprising the remaining proportion. Vaccination status showed that more than half of the children had received at least one vaccine dose. Fever was the most common symptom at the time of admission, followed by cough and dyspnea.These baseline demographic and clinical parameters are presented below (table 1).

Table 1. Demographic and clinical characteristics (n = 79)

Demographic	Frequency	Clinical characteristics	Frequency
Male	56 (70.9%)	Fever	60 (75.9%)
Female	23 (29.1%)	Cough	53 (67.1%)
Vaccinated	47 (59.5%)	Shortness of breath	44 (55.7%)
Unvaccinated	32 (40.5%)	Gastrointestinal symptoms	37 (46.8%)
		Fits	10 (12.7%)
		Mucocutaneous involvement	17 (21.5%)
		Myocarditis	11 (13.9%)

		Hemodynamic instability	5 (6.3%)

Wide variations in coagulation indices, cardiac biomarkers, and inflammatory markers were observed in laboratory measurements, indicating the patients' multisystem involvement. Depending on the clinical severity, several therapy techniques were used. Most patients required intravenous fluid resuscitation, and a high proportion received steroids and IVIG as part of immunomodulatory therapy. Over half of the sample received anticoagulation, mostly with clexane. In few instances, Actemra (tocilizumab) was utilized. Oxygen support varied from low-flow oxygen to invasive breathing, while some patients required inotropic and diuretic medication. Below is Following is a list of the hematological and biochemical evaluation findings and a thorough description of these interventions done (table 2)

Table 2. Laboratory parameters &Treatment modalities (n = 79)

Parameter	Findings	Treatment	Frequency (%)
Neutrophils	0.10 – 24.78	Low-flow nasal oxygen	1 (1.3%)
Lymphocytes	0.44 – 10.06	High-flow nasal oxygen	4 (5.1%)
D-dimer	33.47 – 45,928	Non-invasive ventilation	5 (6.3%)
Ferritin	454.23 ± 110.22	Mechanical ventilation	3 (3.8%)
ALT	139 ± 159.8	Intravenous fluid bolus	59 (74.7%)
CRP	5.46 ± 6.96	Steroids	57 (72.2%)
Procalcitonin	30.41 ± 42.81	Intravenous immunoglobulin (IVIG)	75 (94.9%)
Troponin-I	10 – 4214.9	Anticoagulation (Clexane)	47 (59.5%)
COVID antibody titer	0.40 – 3612	Actemra (Tocilizumab)	11 (13.9%)
IL-6	Reported for limited cases	Diuretics	21 (26.6%)
		Ionotropic support	29 (36.7%)

Most youngsters exhibited remarkable improvement during their hospital stay and were discharged in stable condition. A smaller proportion needed intensive support after deteriorating in spite of treatment. In very few instances, mechanical ventilation was required. The overall mortality rate remained significant. Mean hospital stay was 4.5 days, with ICU stay averaging 2.4 days. Below is a summary of the final results and the condition upon discharge (table 3)

Table 3. Discharge condition and outcomes (n = 79)

Outcome	Frequency (%)
Good condition on discharge	62 (78.5%)
Poor condition on discharge	17 (21.5%)
Required mechanical ventilation	3 (3.8%)
Deaths	17 (21.5%)
Mean hospital stay	4.5 ± 1.6 days
Mean ICU stay	2.4 ± 1.7 days

Discussion

Children between the ages of 6 and 12 made up the biggest afflicted group in this study, accounting for over half of the cases. This age pattern is consistent with several other studies findings that older children were more commonly impacted by MIS-C (11-14). With a male-to-female ratio of 1:1.9, one noteworthy finding in our group was the preponderance of females. The majority of published data shows a bias toward male involvement, with ratios ranging from 1.2:1 to 3.2:1 in various populations (12,13,15,16), despite one study reporting a similar female predominance (1:1.4). This fluctuation implies that gender distribution in MIS-C may be influenced by geographical and demographic variations.

72.2% of the children had elevated COVID antibody titers, and 69.6% had a history of COVID-19 exposure. These results point to a robust immune-mediated post-infectious phase that is in line with the pathophysiology of MIS-C. Our cohort's positive antibody titer frequency is similar to earlier reports, which found that between 19% and 71% of children tested positive (9, 13, 15). When children exhibit with multisystem inflammatory symptoms after COVID-19 exposure, the similarity supports the validity of antibody detection as a diagnostic signal.

Our patient population had noticeably higher levels of inflammatory markers. The most common abnormalities, which reflect the hyperinflammatory aspect of the condition, were elevated CRP (74.7%) and ESR (49.4%). Additionally prevalent were hematologic disorders such as leukocytosis (45.6%) and thrombocytopenia (38%). The published literature shows significantly larger increases for ferritin, D-dimer, and LDH, despite the fact that these markers were increased in 22.8%, 35.4%, and 5.1% of cases, respectively (17). The comparatively lower percentage in our study could be due to variations in illness severity among groups, early presentation, or timely treatment beginning. The existence of cytokine-driven inflammation, which is a hallmark of MIS-C, was further supported by the observation of interleukin-6 increase in 21.5% of cases.

Cardiovascular, gastrointestinal, and mucocutaneous symptoms were the most common clinical presentations. A significant percentage of patients had gastrointestinal involvement, which worsened with age and included vomiting, diarrhea, and abdominal pain. Conjunctival congestion and redness were common mucocutaneous symptoms. Signs related to the heart were especially worrisome: 35.4% of children had hypotension, which is similar to a study where 47% of patients had hypotension at admission (13). Additionally, 7.6% of patients had lower ejection fraction and ventricular dysfunction on echocardiography, underscoring the significance of early cardiac examination in suspected MIS-C cases.

The cohort's needs for respiratory and hemodynamic support differed. Inotropic assistance was needed for about 36.7% of patients, which is comparable with another study that found a similar need (14). More than half of the children in other published data required vasopressors, suggesting regional variations in disease severity (16). The percentage of patients who needed mechanical ventilation was just 3.8%. This relatively reduced respiratory failure burden is consistent with previously reported invasive ventilation ranges of 0–39% (8, 9, 15). Although respiratory compromise was present, it was not the primary feature in the majority of our cases, as evidenced by the 11.4% of patients who had hypoxemia at presentation.

Our study's management techniques were in line with internationally advised therapeutic approaches. Systemic steroids (72.2%) and anticoagulation (59.5%) were the next most used treatment agents, after IVIG (94.9%). Tocilizumab use in 13.9% of instances is indicative of an escalation strategy in certain individuals with chronic inflammation. A number of studies support the use of IVIG, corticosteroids, and anticoagulation as the cornerstone of management, despite the fact that the evidence base for MIS-C treatment is still limited. Standard therapy is guided by similarities with Kawasaki illness (7, 14, 17). These guidelines are supported by our treatment results, especially with regard to quick clinical improvement after early therapy commencement.

Overall, the results of our investigation showed moderate severity. The mean ICU stay was 2.4 days, while the average hospital stay was 4.5 days. Given the severity of the illness, a death rate of 21.5% was noted. One significant finding of this study was that children who met the MIS-C criteria and had a concomitant measles diagnosis had significantly worse outcomes. These kids had a disproportionate incidence of deaths, longer hospital and intensive care unit stays, and a greater requirement for invasive mechanical breathing. Future research should look at this co-infection since it seems to increase the severity of the illness, probably as a result of severe immunological dysregulation.

Limitations

There are a number of limitations to this study. The results may not be as broadly applicable as they could be because it was carried out at a single Centre with a small sample size. Furthermore, knowledge of the possible long-term cardiac, neurological, or immunological effects of MIS-C is limited by the absence of long-term follow-up. Certain biomarkers (such ferritin and IL-6) were evaluated selectively based on clinical necessity, and not all patients had access to serial laboratory testing. To fully comprehend the spectrum and long-term consequences of MIS-C in children, future multicenter trials with longitudinal follow-up are crucial.

Conclusion

Majority of our patients presented with gastrointestinal, hepatic and cardiovascular symptoms. Most of our patients were treated with IVIG, steroids and anticoagulation with positive outcomes. A few children who had coexistent infection with measles required advanced hemodynamic and respiratory support with high mortality rate

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All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed.	