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Multisystem Inflammatory Syndrome in Children with COVID-19 in a Tertiary Care Centre: A Descriptive Cross-sectional Study

Sanjeet Kumar Shrestha,[1] Sumit Agrawal,[2] Amod Rayamajhi,[3] Madhusudan Kayastha,[1] Bulu Wagley Poudel,[2] Ram Hari Chapagain,[2] Ajit Rayamajhi[2]

[1]Department of Pediatrics, Kanti Children's Hospital, Maharajgunj, Kathmandu, Nepal, [2]Department of Pediatrics, National Academy of Medical Sciences, Bir Hospital, Mahabouddha, Kathmandu, Nepal, [3]Bassett Medical Center, Cooperstown, New York, USA.

ABSTRACT

Introduction: Multisystem inflammatory syndrome in children is a rare and serious complication of COVID-19. Multisystem inflammatory syndrome in children presents with systemic inflammation, end-organ dysfunction, shock, and elevated inflammatory markers and abnormal complete blood counts requiring intensive care. Clinical features and outcomes are less well-known in children. The aim of the study was to find out the prevalence of Multisystem inflammatory syndrome in children with COVID-19.

Methods: A descriptive cross-sectional study was conducted among children diagnosed with COVID-19 in Kanti Children's Hospital over one year from 01 January 2021 to 31 December 2021 after receiving ethical approval from the Institutional Review Committee (Reference number: 27/2020-21). Children aged 1 month to 14 years with COVID-19 were included in the study, and those who failed to give consent were excluded from the study. A convenience sampling method was used. An analysis was conducted on the demographics, clinical characteristics, laboratory results, treatment, and outcome of every kid diagnosed with multisystem inflammatory syndrome among children linked to COVID-19. Point estimate and 95% Confidence Interval were calculated.

Results: Among 315 COVID-19 patients, multisystem inflammatory syndrome in children was found in 57 (18.09%) (13.84-22.35, 95% Confidence Interval). Thirty seven (64.91%) of the patients with multisystem inflammatory syndrome in children had gastrointestinal symptoms. Shock at initial presentation was also present in 25 (43.86%) patients. Most 37 (64.91%) of them were treated with intravenous immunoglobulin and steroids, and 20 (35.08%) patients died.

Conclusions: Multisystem inflammatory syndrome in children is one of the most common complications of COVID-19 in children. Most of the patients of multisystem inflammatory syndrome in children present with gastrointestinal manifestations. Other features at presentation were hyperinflammation, hypoalbuminemia, and shock. The majority of patients required pediatric intensive care unit admission and oxygen supplementation

Keywords: *COVID-19; Kawasaki disease; multisystem inflammatory syndrome.*

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a rare and serious complication of COVID-19. MIS-C presents with systemic inflammation, end-organ dysfunction, shock, and elevated inflammatory markers and abnormal complete blood counts requiring intensive care.[1-4]

In April 2020, eight children, who were previously well, were reported for the first time in the United Kingdom with features similar to Kawasaki disease (KD) or toxic shock syndrome and later termed multisystem inflammatory syndrome in children (MIS-C).[5] Nepal reported MIS-C for the first time on September 19, 2020.[6] There have been very few studies done about MIS-C in Nepal, and Kanti Children's Hospital being the only tertiary care government hospital, so we decided to conduct this study.

Correspondence:

Dr. Sanjeet Kumar Shrestha
Department of Pediatrics, Kanti Children's Hospital, Maharajgunj, Kathmandu, Nepal
Email: ssanjeet74@gmail.com
Phone: +977-9851125282.

The aim of the study was to find out the prevalence of Multisystem inflammatory syndrome in children with COVID-19.

METHODS

A descriptive cross-sectional study was conducted among children diagnosed with COVID-19 in Kanti Children's Hospital, Maharajgunj, Kathmandu, Nepal over one year from 01 January 2021 to 31 December 2021 after obtaining ethical approval from the Institutional Review Committee (IRC) (Reference number: 27/2020-21). Children aged 1 month to 14 years who fulfilled the diagnostic criteria of COVID-19 were included in the study. Children who did not meet the criteria or failed to give consent were excluded from the study. Convenience sampling was used. The sample size was calculated using the following formula:

$n = Z^2 \times p \times q / e^2$

$= 1.96^2 \times 0.5 \times 0.5 / 0.06^2$

$= 267$

Where,

n = minimum required sample size

Z = 1.96 at 95% Confidence Interval (CI)

p = prevalence taken as 50% for maximum sample size calculation

q=1-p

e= margin of error, 6%

The sample size calculated was 267. However, 315 patients were taken for the study.

In order to diagnose MIS-C in COVID-19 patients, we have employed MIS-C criteria.[7] A pre-made proforma was used to gather demographic information, clinical data, and biochemical values from individuals who satisfied the diagnostic requirements. Age, sex, height, weight, and the child's address were among the demographic information provided. Blood pressure (BP) centile, conjunctivitis, skin rash, mucositis, extremity swelling, cough, shortness of breath, decreased urine output, jaundice, fever, loose stools, abdominal pain, vomiting, and blood in the stool were among the clinical parameters that were included. Laboratory investigations included hemoglobin, total leukocyte count, platelet count, bilirubin, transaminases, prothrombin Time (PT), international normalized ratio (INR), activated thromboplastin time (aPTT), total protein, serum albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, fibrinogen, ferritin, procalcitonin, BNP, troponin I and COVID 19 antibody titre. Results of COVID-19 RT-PCR and COVID-19 antigen tests were also included. Echocardiography was performed routinely in all patients to look for MIS-C. Hence, non-tapering of coronary arteries, increased echogenicity of coronaries, and dilatation of coronary arteries on echocardiography were also recorded. The data was then entered into an MS Excel spreadsheet. Data was then analyzed using SPSS version 25.0. Point estimate and 95% Confidence Interval were calculated. Binary data were expressed in the form of numbers and percentages, and continuous data in the form of mean and standard deviation.

RESULTS

Among 315 patients, MIS-C was found in 57 (18.09%) (13.84-22.35, 95% CI). 37 (64.91%) of the patients with Multisystem Inflammatory Syndrome in Children had gastrointestinal symptoms. Vomiting was seen in 23 (40.35%), loose stools in 16 (28.07%), and abdominal pain in 10 (17.54%). Skin rash was seen in 26 (45.61%) (maculopapular in 22 (93.00%), petechial in 1 (2.00%), and polymorphous 3 (5%). (Table 1).

Table 1. Clinical Characteristics of the study population (n= 57).

Clinical Characteristics	n (%)
Duration of fever	
≤ 3 days	16 (28.07)
4-7 days	30 (52.63)
> 7 days	11 (19.29)
Presence of Gastrointestinal Symptoms	37 (64.91)
Conjunctivitis	21 (36.84)
Presence of skin rash	26 (45.61)
Mucositis	9 (15.78)
Extremity swelling	8 (14.03)
Cough	11 (19.29)
Shortness of breath	10 (17.54)
Decreased urine output	1 (1.75)
Jaundice	7 (12.28)
Reported contact with a COVID-19 Positive individual	11 (19.29)
Blood Pressure Centile	
< 5th centile	25 (43.86)
5th-95th centile	32 (56.14)

Among 57 MIS-C patients, elevated Troponin I was observed in 8 (14.03%), echocardiographic abnormality in 9 (15.78%), including dilated coronary arteries in 4 (7.01%). Markers of

inflammation, such as mean ESR was 35 mm/1st hour, CRP 9.73 mg/dl, D-dimer 1587.5 ng/ml, fibrinogen 436 mg/dl, ferritin 542.5 ng/ml, and procalcitonin 2.72 ng/ml, were also elevated, which was the hallmark of MIS-C. Our findings of cardiac involvement in 15.78% and dilated coronary artery in 7.01%.

Out of the 57 MIS-C children, 44 (77.19%) were diagnosed as MIS-C only, whereas 11 (19.29%) had MIS-C with KD-like presentation. The mean length of hospital stay was 11.7 ± 9.5 days. Intravenous immunoglobulin (IVIG) with steroids was administered to 37 (64.91%) of these children as initial therapy. Defervescence of fever was seen in 30 (52.63%) after 1st dose of IVIG (Table 2).

Table 2. Diagnosis, treatment, and outcome of study population (n = 57).

Variable	n (%)
Final diagnosis	
MIS-C only	44 (77.19)
MIS-C with KD-like	11 (19.29)
MIS-C with Acute Liver Failure (ALF)	1 (1.75)
MIS-C with Hemophagocytic Lymphohistiocytosis (HLH)	1 (1.75)
Initial Treatment of Patients	
IVIG alone	9 (15.78)
IVIG + Steroids	37 (64.91)
Steroids alone	8 (14.03)
None	3 (5.26)
Defervescence of fever after 1st dose of IVIG	30 (52.63)
Relapse treatment	
Done	10 (21.74)
Not done	6 (13.04)
Modality of relapse treatment	
IVIG alone	1 (6.25)
Steroids alone	9 (56.25)
Need for PICU admission	40 (70.17)
Need for supplemental oxygen	35 (61.40)
Need for mechanical ventilation	20 (35.08)
Outcome	
Discharged	37 (64.91)
Died	20 (35.08)

Most 33 (57.89%) of the patients were from Bagmati province. A total of 57 patients were recruited in the study. The mean age at the time of presentation was 6.7±4.4 years (Table 3).

Table 3. Demographic characteristics of study population (n = 57).

Demographic Characteristics	n (%)
Age	
1 month- 5 years	20 (35.08)
5-10 years	23 (40.35)
10-14 years	14 (24.56)
Sex	
Male	41 (71.93)
Female	16 (28.07)
Address (Province)	
Koshi	5 (8.77)
Madesh	8 (14.03)
Bagmati	33 (57.89)
Gandaki	2 (3.51)
Lumbini	5 (8.77)
Far West	4 (7.01)
Karnali	-

DISCUSSION

Among 315 patients, MIS-C was found in 57 (18.09%). The clinical manifestations of COVID-19 are predominantly fever and mild upper respiratory tract symptoms. In this study, we noted that GI complaints were present in 37 (64.91%) of children. Similarly, others have also found GI manifestations to be present in 71-92% of children affected with MIS-C.[8-11] In this study, vomiting and loose stools were the predominant gastrointestinal features present in 23 (40.35%) and 16 (28.07%), respectively, while abdominal pain was present in only 10 (17.54%). However, abdominal pain was the predominant feature (> 70%) in a study conducted in the United States of America.[3] This explains the earlier described notion that gastrointestinal manifestations are predominant in children with MIS-C. Involvement of the gastrointestinal tract and liver in COVID-19 is mainly due to the characteristic distribution of Angiotensin I converting enzyme 2 (ACE2).[12] ACE2 is the target entry receptor for both SARS-CoV and SARS-CoV-2, and is mainly expressed in lung alveolar type 2 cells, epithelial cells of the esophagus, stomach, ileum, colon, and rectum, liver cholangiocytes, and renal proximal tubules.[13]

The mean age of our study population was 6.7 years. The age was similar to previous studies, which reported

8.6 years and 9 years.[10,14] Three-quarters of the affected were boys, which was also similar to previous studies.[9,10] The majority (57.89%) of the children were from Bagmati Province, which could possibly have been because the hospital was located in the same province.

Conjunctivitis was present in one-third, and skin rash in almost half of our patients. Skin rash was predominantly maculopapular. Conjunctivitis has also been reported in half of the patients, and rash in 70% in the United States of America previously.[3] Both respiratory symptoms and reported contact with a COVID-19 positive individual were seen in 19.29%. Respiratory symptoms have been reported in only 10% of children previously.[3,10] In this study, BP was <5th centile in 43.86% of children at presentation. Similarly, around 50% of children have been reported in shock at presentation in the past in the USA and Brazil. [2,3]

Regarding laboratory parameters, complete blood counts and renal function tests were within normal limits. Amongst liver function parameters, mean albumin was 2.3 ± 0.6 g/dl. Hypoalbuminemia was significantly associated with mortality in our study. Hypoalbuminemia has also been reported to be associated with a greater need for PICU admissions in the past.[15] Some have also reported hypoalbuminemia to be significantly associated with increased mortality.[16] Markers of inflammation, such as mean ESR was 35 mm/1st hour, CRP 9.73 mg/dl, D-dimer 1587.5 ng/ml, fibrinogen 436 mg/dl, ferritin 542.5 ng/ml, and procalcitonin 2.72 ng/ml, were also elevated, which was the hallmark of MIS-C. Our findings of cardiac involvement in 15.78% and dilated coronary artery in 7.01% were much less than 62.5% and 33.3% respectively, reported previously.[17]

In this study, MIS-C with non-KD-like presentation was observed in 77.19%, and KD-like presentation was seen in 19.29%. Additionally, two patients of MIS-C had ALF and HLH each. Similar to our findings, a study conducted in Iran also reported a high proportion (79.5%) of MISC without KD-like presentation in their children.[18] On the contrary, MIS-C with KD-like features have been reported in 45-80% in previous studies.[19-21] This low occurrence of KD-like features in our study may have been because of the relatively darker skin of our patients, which may have masked the rashes.

In this study, IVIG alone was administered as initial treatment in 15.78%, a combination of steroids (IV methylprednisolone followed by oral prednisolone) and IVIG in 64.91%, only steroids in 14.03%, while 3% didn't receive any treatment. The treatment was based on the standard guideline recommended at that time.[22,23] From the time of initiation to completion of the study, there have been many changes in the treatment protocol of MIS-C because of newer evidence reported by different researchers of this novel illness. Hence, some minor differences in management could have occurred in some cases. Some patients received only steroids because of financial constraints.

Defervescence of fever after the first dose of IVIG was seen in 52.63% of children. Relapse was treated in 10 (21.74%) patients. Steroids (namely IV methylprednisolone followed by oral prednisolone) were used for treatment for 9 out of 10 patients who had relapse, and the remaining 1 patient was managed with IVIG alone. This was again based on existing standard guidelines.[22,23] PICU admission was needed in 70.17%, supplemental oxygen in 61.40%, and mechanical ventilation in 35.08%. On the contrary, mechanical ventilation was required in only 17.6% of children in the United States of America.[24] In South Africa, only 40% of children required PICU admission, 38.2% of children required oxygen therapy, and 11.8% required mechanical ventilation.[25] These disparities may have been due to the differences in sample size and demographics of the study population. In our study, the mortality was 35.08%. The mortality was much higher than 1.9%- 4.9% reported in Europe and America, which may have been due to delayed presentation, more severe disease, and limited available resources.[24, 26, 27]

As it was a single-centered study, its findings can't be generalized to the entire population.

CONCLUSIONS

MIS-C is one of the most common complications of COVID-19 in children. Most of the patients of Multisystem Inflammatory Syndrome in Children present with gastrointestinal manifestations. Other features at presentation were hyperinflammation, hypoalbuminemia, and shock. A quarter of patients had MIS-C with KD-like features. Most of them were treated with IVIG and steroids. The majority of children required PICU admission and oxygen supplementation. One-third of the patients died.

Conflict of Interest: None

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