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# Acute kidney injury in children with covid-19 related Multisystem Inflammatory Syndrome in Children (MIS-C)

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## Abstract

**Introduction: Although children with coronavirus-19 disease generally experience mild disease, a subset of them develop Multisystem Inflammatory Syndrome(MIS-C). There is relative rarity of literature regarding Acute Kidney Injury (AKI) in MIS-C. We aim to characterize the clinical features, laboratory findings and therapies for AKI in MIS-C in our setup.**

**Materials and Methods: This was a 2-year study, with children who had AKI and met the criteria for MIS-C based on CDC guidelines.**

**Results: There were a total of seven cases (age ranging between 4 years to 20 years). Persistent fever was present in all patients. Six had vomiting/diarrhoea along with rashes and/or swelling of hands. Myocardial involvement was seen in four, respiratory in two and musculoskeletal in one patient. Oropharyngeal swab for SARS-Cov2 RNA was negative in all. Anticovid antibodies were positive in five and two had a history of contact with COVID-19 patients. AKI Stage 1 was present in 3, stage 2 and 3 in 2 patients each. Neutrophilia with lymphopenia was seen in all and thrombocytopenia in 4 patients. Laboratory findings for inflammatory markers showed marked elevation of C-reactive protein, ferritin, procalcitonin, ESR, fibrinogen, LDH and D-Dimer. The patients were treated with a combination of steroids, IVIg and inotropic support wherever needed. All of the patients recovered with a median duration hospital stay of 7(IQR 5) days.**

**Conclusion: Children with covid-19 infection should be carefully followed for MIS-C. Although children with MIS-C develop AKI, most of them have full clinical recovery. The long term prognosis of this syndrome is currently unknown and require extensive studies.**

***Keywords:*** Acute Kidney Injury (AKI); Covid-19; Multi-inflammatory response syndrome in children.

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## Introduction

Children with Coronavirus Disease 2019 (COVID-19) usually present with a mild upper respiratory illness. However in late April, 2020, there were reports of severely ill pediatric patients presenting in hyper inflammatory shock with multiorgan involvement. The children also manifested with persistent fever, rash, conjunctivitis, peripheral edema, and gastrointestinal symptoms. This acute condition was known as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 by Royal College of Paediatrics and Child Health (RCPCH) and Multisystem Inflammatory Syndrome in Children (MIS-C) by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) [1]. It is important to differentiate these patients from Kawasaki Disease (KD) or Toxic Shock Syndrome (TSS) [2]. The incidence of Acute Kidney Injury (AKI) has been found to be more common in children who met diagnostic criteria for PIMS-TS than covid-19 patients with acute infection [3]. However, studies describing the incidence and characteristics of renal complications in MIS-C (2,3,9) are limited [4]. We aim to describe our experience regarding acute kidney injury in children with multisystem inflammatory syndrome in our population. We also aimed to study the long term outcome of these patients for which the literature is scarce.

## Materials and Methods

### *Study population and data collection*

This was a two-year study with patients from GMC Srinagar, its associated hospitals and Shifa Medical Centre, Srinagar.

Children <21 years old who had AKI and met the criteria for MIS-C based on CDC guidelines were included in the study.

### *Exclusion criteria*

Patients who had a clinical presentation of MIS-C but did not meet the Centres for Disease Control and Prevention (CDC) Case Definition Criteria.

### *Data source and variables*

Clinical and demographic data, laboratory data, peak inflammatory marker values and treatment received by the patients were recorded from the hospital records.

### *Definitions*

The CDC characterizes MIS-C by individual ≤ 21 years of age presenting with persistent fever, laboratory markers of inflammation, with evidence of severe illness requiring hospitalization and multi-organ (≥ 2) involvement (e.g. cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) and who tested positive for current or recent SARS-CoV-2 infection or had serologic confirmation of exposure to COVID-19 within 4 weeks of onset of symptoms [5].

Acute Kidney Injury (AKI) was defined as an abrupt decrease in renal function occurring within 7 days [6]. AKI was classified according to AKIN staging system in three stages: AKIN Stage 1-Serum creatinine increase ≥ 26.5 µmol/l (≥ 0.3 mg/dl) or increase to 1.5-2.0 fold from baseline, AKIN Stage 2-Serum creatinine increase >2.0-3.0-fold from baseline and AKIN Stage 3-Serum creatinine increase > 3.0-fold from baseline or serum creatinine ≥ 354 µmol/l (≥ 4.0 mg/dl) with an acute increase of at least 44 µmol/l (0.5 mg/dl) or need for renal replacement therapy [7].

### *Statistical Analysis*

The statistical analysis was done using SPSS Version 23.0. (IBM Corp., Armonk, NY, USA). Continuous variables, reported as mean or median (depending on the normality of data) were compared using t test, one-way Analysis of Variance (ANOVA), Wilcoxon rank-sum methods as appropriate.

## Results

Our group included seven patients admitted during the defined period and meeting criteria for MIS-C. The median age was 11 years (IQR 7 years) with youngest patient of 4 years of age and oldest being 18 years. There was no significant gender preponderance with 4 females and 3 males. SARS-CoV-2 seropositivity was present in 5% patients. Oropharyngeal swabs for SARS-Cov2 RNA were negative in all the patients. Five patients had negative serology but met CDC criteria for MISC with history of exposure within 4 weeks. Persistent fever was present in all patients. Six children had vomiting/diarrhoea along with rashes and/or swelling of hands. Myocardial involvement was seen in four, respiratory in two and musculoskeletal in one patient. No one had any have underlying kidney disease prior to admission.

AKI Stage 1 was present in 3 (42.8%), stage 2 and 3 in 2 patients (28.5%) each. Neutrophilia with lymphopenia was seen in all the patients and thrombocytopenia in 4 (57.1%) patients. Laboratory findings for inflammatory markers showed marked elevation of C-reactive protein (mean 87.6 ± 72.1 mg/l), ferritin (mean 810 ± 224 ng/ml), procalcitonin (mean 4.9 ± 2.1 ng/ml), ESR (mean 64.6 ± 21.9 mm/hr), fibrinogen (690 ± 142.1 mg/dl), LDH (mean 578.2 ± 370.1 U/L) and d-Dimer (mean 7.8 ± 9.4 µgFFU/ml).

The patients were treated with a combination of steroids, IVIg and inotropic support wherever needed. All of the patients recovered with a median duration hospital stay of 7 (IQR 5) days. These patients were followed up for minimum 1-year period and did not show rise in creatinine in any of the patient. The summary of all the cases (Table 1) and case wise description of each case is tabulated (Table 2).

| | | **Number (Percentage)** |
|---|---|---|
| **Median age (years)** | | 11 (IQR 7) |
| **Male : Female** | | 01:01.3 |
| **Symptoms** | Fever | 7 (100%) |
| | Gi Symptoms | 6 (85.7%) |
| | Mucocutaneous Symptoms | 6 (85.7%) |
| | Cardiac | 4 (57.1%) |
| | Respiratory | 2 (28.5%) |
| | Musculoskeletal | 1 (14.2%) |
| **AKI stage** | AKIN 1 | 3 (42.8%) |
| | AKIN 2 | 2 (28.5%) |

| | | |
|---|---|---|
| | AKIN 3 | 2 (28.5%) |
| **Hematological parameters** | Neutrophilia | 7(100%) |
| | Lymphocytopenia | 7(100%) |
| | Thrombocytopenia | 4 (57.1%) |
| **Mean ESR** | | 64.6 ± 21.9 mm/hr |
| **Mean CRP** | | 87.6 ± 72.1 mg/l |
| **Mean ferritin** | | 810 ± 224 ng/ml |
| **Mean procalcitonin** | | 4.9 ± 2.1 ng/ml |
| **Mean fibrinogen** | | 690 ± 142.1 mg/dl |
| **Mean LDH** | | 578.2 ± 370.1 U/L |
| **Mean D-Dimer** | | 7.8 ± 9.4 µgFFU/ml |
| **Mean IL-6** | | 138.9 ± 79.8 pg/ml |
| **Mean albumin** | | 2.8 ± 0.6 gm/dl |
| **Treatment** | Antibiotics | 7 (100%) |
| | Steroids | 5 (71.4%) |
| | IVIg | 4 (57.1%) |
| | Aspirin | 2 (28.5%) |
| | Heparin | 2 (28.5%) |
| | Oxygen | 2 (28.5%) |
| | Inotropic support | 2 (28.5%) |
| | HD | 2 (28.5%) |

***Table 1:*** Summary of our cases.

| | | **Case 1** | **Case 2** | **Case 3** | **Case 4** | **Case 5** | **Case 6** | **Case 7** |
|---|---|---|---|---|---|---|---|---|
| **Age** | | 4 | 15 | 18 | 12 | 10 | 8 | 11 |
| **Sex** | | F | F | F | M | M | F | M |
| **Lag period (Days)** | | 9 | 17 | 15 | 21 | 20 | 24 | 14 |
| **Presenting symptoms** | Fever | P | P | P | P | P | P | P |
| | GI | A | P | P | P | P | P | P |
| | Mucocutaneous | A | P | P | P | P | P | P |
| | Cardiac | P | A | P | A | A | P | P |
| | Respiratory | A | A | P | P | P | A | A |
| | Musculoskeletal | A | A | A | P | A | A | A |
| **ESR** mm/hr | | 90 | 92 | 75 | 60 | 56.5 | 50 | 70 |
| **CRP** mg/l | | 41.3 | 90 | 9.8 | 24.7 | 211 | 149 | 100 |
| **Ferritin** ng/ml | | 980 | 950 | 798 | 920 | 620 | 970 | 1015 |
| **Procalcitonin** ng/ml | | 4.6 | 3.9 | 4.2 | 3.9 | 10.1 | 4.6 | 4.4 |
| **Fibrinogen** mg/dl | | 780 | 820 | 850 | 750 | 693 | 794 | 694 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **LDH** | | 487 | 574 | 291 | 1200 | 687 | 339 | 658 |
| U/L | | | | | | | | |
| **D-Dimer** | | 4.5 | 6.5 | 4.1 | 3.5 | 5.1 | 23 | 6.8 |
| µgFFU/ml | | | | | | | | |
| **IL-6** | | 67 | 48 | 127 | 203 | 157 | 274.5 | 96 |
| pg/ml | | | | | | | | |
| **Albumin** | | 2.5 | 3.5 | 2.8 | 2.1 | 2.4 | 3.1 | 3.8 |
| gm/dl | | | | | | | | |
| **Treatment** | Antibiotics | Received | Received | Received | Received | Received | Received | Received |
| | Steroids | Received | Received | Received | Received | Received | Received | Received |
| | IVIg | | | Received | Received | Received | Received | |
| | Aspirin | Received | | | | | | |
| | Heparin | | | Received | | | Received | |
| | Oxygen | | | Received | Received | | | |
| | Inotropic support | | | Received | Received | | | |
| | HD | | | | Received | | Received | |

***Table 2:*** Case wise description of all the cases. **Note:** Present (P); Absent (A).

## Discussion

Covid related Multisystem Inflammatory Response in Children (MIS-C) is a rare complication which occurs in < 1% of pediatric covid-19 patients and Acute Kidney Injury (AKI) occurs in 10%-60% of these patients [8,9]. Although there have been only a limited studies describing AKI in MIS-C3, the number of published data is increasing. We, in this research, state our experience of paediatric covid-19 related multi inflammatory syndrome acute kidney injury in our part of country.

The median age of presentation in our study was 11 years with no gender predilection. The median age in other studies also range from 9 years-10 years [3,4,10]. Some studies have indicated an age of more than 7 years characteristic when compared to KD [11].

The mean duration from onset of symptoms to exposure was 17days. This lag period is hypothesized to be due to its post-infectious nature.

Fever was present in all the patients. The most common systems involved were gastrointestinal, mucocutaneous and cardiac. These results are seen in other studies as well. Also the predominance of cardiac manifestations in these patients is striking [3].

Only one patient had 2+ proteinuria on urinalysis and two had increased red blood cells. Other patients had essentially normal urine examination findings [12]. The authors argued that the findings such as low cardiac output and absence of urinary abnormalities in most of these patients suggest a pre-renal pathogenesis in most of these patients. Also the fact that few of these patients have urine abnormalities suggest a multifactorial pathogenesis rather than any single cause in these patients-including both pre-renal and renal parenchymal injury. The pathogenesis of AKI although multifactorial is mostly contributed by renal hypoperfusion caused by hyper inflammatory state and predisposition to capillary leak syndrome, low cardiac output and dehydration caused by vomiting and diarrhoea [12]. Imbalance in rennin-angiotensin-aldosterone system which leads to glomerular dysfunction, endothelial dysfunction, complement and coagulation pathway activation, renal vascular injuries, drug toxicity and organ cross-talk mechanisms are other factors which contribute to acute kidney injury in these patients [9].

The hematological abnormalities in our patients included neutrophilia and lymphocytopenia. Ahmed et al., in a multisystemic review found that 95% of the 662 cases (2 standard deviations) had an elevated neutrophil percent. Feng et al., in a meta-analysis of 4911 COVID-19 patients reported that severe patients present with neutrophilia along with lymphocytopenia [13]. They argued that the degree of separation between the two cell types may correlate with the severity of inflammation. Many studies have also found an association between the percentage of neutrophils, lymphocytes and the neutrophil to lymphocyte ratio to severity of disease. These results could not be replicated by us due to limited number of cases in our study.

The markers of inflammation in these patients were markedly elevated. These markers are of particular importance in distinguishing this condition from Kawasaki disease along with other factors like age of the patient, degree of inflammation and myocardial injury and Anti-SARS-CoV-2 IgG titres [14,15].

The short term as well as long term outcome of these patients was favourable. The mean hospital stay was of 7days. These patients improve with a combination of ivIg, steroids and inotropic support. The fluid resuscitation, however, in patients should include careful use of IV fluids keeping in mind that most of these patients have some degree of cardiac dysfunction which may be worsened by aggressive fluid resuscitation [12]. These patients had a good prognosis in other studies as well. However, the long-term squeal from this disease is currently

unknown [2]. We tried to follow these cases for a minimum period of one year and all these cases showed complete recovery.

## Conclusion

Children with covid 19 infection should be carefully followed for MIS-C. Although children with MIS-C develop AKI, most of them have full clinical recovery. Although both short-term as well as long term follow-up of these patients is favourable, the data regarding their follow-up is still limited and further long term studies are required to fully understand this disease.

## Limitations

The limitations of this study included limited number of patients and lack of baseline serum creatinine values to accurately define and stage AKI. We could not comment upon the histopathological features and renal immune- complex deposition in these patients as none of our cases underwent kidney biopsy.

## Strengths

This study provides detailed description of MISC- AKI in our set-up. Also, these patients had a minimum two years of the follow-up data available.

## Ethical Approval

This was not sought as it did not involve any active participation of the patients. Few patients whose data was analysed could also not be contacted further. The patients were de-identified and waiver of their consent did not adversely affect the rights and welfare of the participants.

### Authors' Contribution

All the authors contributed to study conception, design, editing, reviewing and final approval of article. Zahir Z and Wani AS contributed to data acquisition, analysis, interpretation, and writing of the article.

### Presentation at Conference

This paper was presented in an international conference "International Conference on Coronaviruses: Past, Present, and Future," held in May, 2022 at SKAUST, Kashmir, India.

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