Kidney360 Publish Ahead of Print, published on February 3, 2021 as doi:10.34067/KID.0005372020



# Acute Kidney Injury in COVID-19-associated Multisystem Inflammatory Syndrome in Children (MIS-C)

Marissa Lipton[1], Ruchi Mahajan[1], Catherine Kavanagh[1], Carol Shen[1], Ibrahim Batal[2], Samriti Dogra[1], Namrata G. Jain[1], Fangming Lin[1], Natalie S. Uy[1]

[1]Division of Pediatric Nephrology, Department of Pediatrics

[2]Department of Pathology and Cell Biology

Columbia University Vagelos College of Physicians and Surgeons

New York, NY 10032

USA

Corresponding author:

Natalie S. Uy, MD

Division of Pediatric Nephrology

Department of Pediatrics

622 West 168th Street, PH 17-102B

Columbia University Vagelos College of Physicians and Surgeons

New York, NY, 10032

Email: nsu1@cumc.columbia.edu

Phone: 212 305-5825

Fax: 212 342-0518

**Key Points**

- AKI was a common finding among pediatric patients hospitalized with COVID-19 associated MIS-C.
- Older age, increased inflammation, and left ventricular systolic dysfunction may be risk factors for AKI in children with MIS-C.
- While children with MIS-C may develop AKI, our study suggests most experience mild disease, swift resolution and promising outcome.

**Abstract**

**Background:** Multisystem Inflammatory Syndrome in Children (MIS-C) is a recently identified entity in association with COVID-19. Acute kidney injury (AKI) has been widely reported in patients with primary COVID-19 infection. However, there is a paucity of literature regarding renal injury in MIS-C. We aim to characterize AKI in MIS-C in this cohort identified at a major children's hospital in New York City during the COVID-19 pandemic.

**Methods:** We conducted a retrospective cohort study of children 0-20 years old admitted to Morgan Stanley Children's Hospital (MSCH) between April 18$^{th}$ and September 23$^{rd}$, 2020. Patients were included if they met criteria for MIS-C based on CDC guidelines. All patients were evaluated for the presence of AKI, and AKI was staged according to KDIGO criteria.

**Results:** Of the 57 children who met inclusion criteria, 46% (26/57) were found to have AKI. The majority of patients, 58% (15/26), were classified as KDIGO Stage 1. AKI was present upon admission in 70% of those identified. All patients had resolution of AKI at discharge, with 61% achieving recovery by day 2. One patient required dialysis. When

compared to those without renal injury, the AKI cohort was older ($p < 0.001$) and with higher median peak values of CRP ($p <0.001$), IL-6 ($p <0.05$), ferritin ($p < 0.001$), and procalcitonin ($p <0.05$). More patients with AKI had left ventricular systolic dysfunction ($p < 0.001$) and lymphopenia ($p <0.01$), when compared to those without AKI. No differences in Body Mass Index or sex were found.

**Conclusion**: While children with MIS-C may develop AKI, our study suggests most experience mild disease, swift resolution, and promising outcome**.** Older age, increased inflammation, and left ventricular systolic dysfunction may be risk factors. Our study highlights the substantial differences in epidemiology and outcomes between AKI associated with pediatric MIS-C versus primary COVID-19 infection.

## Introduction

As the COVID-19 pandemic continues around the world, manifestations of infection by the SARS-CoV-2 virus in children continues to be an active area of research. A syndrome currently named “Multisystem Inflammatory Syndrome in Children” (MIS-C) was first described in late April 2020 by clinicians in the United Kingdom, who recognized previously healthy children presenting with a severe inflammatory syndrome after testing positive for concurrent or recent infection of COVID-19 (1). The syndrome was soon thereafter recognized in the US, and as of December 4, 2020, 1288 American cases had been identified by the Center for Disease Control (CDC) (2).

The CDC characterizes MIS-C by persistent fever, laboratory markers of inflammation, with evidence of severe illness requiring hospitalization and multi-organ involvement (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic)(2). Common manifestations include diminished left ventricular systolic function with or without coronary artery changes (3-5). The affected individual must be < 21 years old and have had an exposure to a confirmed or suspected COVID-19 case. Patients may exhibit some or all features of Kawasaki Disease (1-3).

Acute kidney injury (AKI) has been widely reported in patients with primary COVID-19 infection (6, 7). Recently, a multicenter study reported on the prevalence of AKI amongst critically ill children with primary COVID-19 infection (8). However, there have been limited studies describing the incidence and characteristics of renal complications in MIS-C (2, 3, 9). Previous experience taking care of adult COVID-19 patients in our center has given us the opportunity to be able to highlight the substantial

differences in epidemiology and outcomes in patients with AKI in MIS-C in contrast to AKI from primary COVID-19 infection (10). Here, we report the characteristics of AKI in children diagnosed with MIS-C in a large, tertiary, free-standing children's hospital in New York City, one of the early epicenters of the COVID-19 pandemic in the United States. To our knowledge this is the first study to date specifically focused on describing the characteristics of pediatric AKI in MIS-C.

## Materials and Methods

### Study Population and Data Collection

A retrospective chart review was performed to identify children < 21 years of age who were admitted to Columbia University Irving Medical Center/Morgan Stanley Children's Hospital (MSCH) of the NewYork-Presbyterian System with symptoms and clinical findings consistent with MIS-C between April 18, 2020 to September 23rd, 2020. Chart review was carried out with approval of the Institutional Review Board. Patients were included if they met criteria for MIS-C, as defined according to CDC guidelines (2). Diagnosis criteria included fever, laboratory evidence of inflammation, with multisystem (≥ 2) organ involvement, as detailed in Table 1. Patients either tested positive for current or recent SARS-CoV-2 viral infection by RT-PCR, serology, or antigen test; or had exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. Patients with positive PCR testing were distinguished from primary COVID-19 infection by lack of pulmonary involvement or otherwise did not fit the clinical diagnosis of primary infection.

Demographics including age and sex were recorded for all patients. As data review was limited to the electronic medical record, race was not consistently

documented. Patients were however listed as Hispanic or Non- Hispanic ethnicity. Serum creatinine values, as measured by the enzymatic method, were noted at both peak and nadir of hospitalization. Given lack of previous laboratory values for most children, hospitalization nadir was treated as patients' baseline creatinine. Additional clinical criteria including BMI percentile as well as other laboratory values, such as peak value of inflammatory markers, were reviewed for each patient.

AKI was defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Classification that is applicable to both adult and pediatric populations (11, 12). Given the inconsistencies in documentation regarding urine output, patients were classified based on serum creatinine alone, as detailed in Table 2. Factors potentially contributing to AKI were recorded and included: exposure to nephrotoxic medications commonly used in our hospital (i.e., aminoglycosides, trimethoprim/sulfamethoxazole, vancomycin, acyclovir, nonsteroidal anti-inflammatory drugs, iodine-based contrast for imaging, and calcineurin inhibitors), hypotension requiring vasopressors, and echocardiographic findings of decreased left ventricular systolic function. Two time points were recorded: Time to peak creatinine (day of hospitalization) as well as time to recovery (days) defined as return to baseline/nadir creatinine. The presence of significant proteinuria was defined as ≥ 2+ protein (100 mg/dL) on urinalysis. Patients for whom certain data were unavailable or missing were excluded from analysis regarding that factor. Data whose values were outside a laboratory reference range were analyzed as the closest value (minimum or maximum) within range.

**Statistical Analysis**

Statistical analyses were performed using Prism 7 (Graphpad Inc, San Diego, CA) and SPSS Statistics, Version 26.0. Continuous data were presented as median and range. Continuous variables were compared using the Mann-Whitney test while categorical variables were compared using Fisher's Exact test. Cox proportional hazards model univariate analysis was performed. Significance was defined as $p<0.05$. No covariables were found to be significant and therefore we did not proceed with multivariate analysis.

**Results**

Our cohort included 58 patients admitted during the defined period and meeting criteria for MIS-C. One patient was identified as meeting criteria for MIS-C and developed severe AKI while at an outside hospital which had resolved prior to transfer to our center. Data during that hospitalization was limited, and therefore, this patient was excluded from our group.

The majority of patients (74%) were negative for active SARS-CoV-2 infection by PCR at time of hospitalization; the remaining 26% had positive PCR results. Additionally, only 52 patients were tested for SARS-CoV-2 antibodies, 88% of which had positive serology. Five patients had negative serology but met CDC criteria for MIS-C with suspicion of exposure. Five patients were not tested for antibodies and one patient had indeterminant serology, but all met CDC criteria for MIS-C (Figure 1).

AKI occurred in 26 of the 57 (46%) patients: stage 1 AKI (n = 15, 58%), stage 2 AKI (n = 7, 27%), and stage 3 AKI (n = 4, 15%). Continuous renal replacement therapy was initiated in only one patient, due to worsening uremia. The majority of AKI patients (70%) presented with AKI at the time of admission, and an additional 27% developed AKI within 24-72 hours of hospitalization. All patients with AKI recovered renal function,

with 19% recovering within 24 hours. Most patients (75%) with stage 3 AKI required more than 3 days to recover. Comparatively, only 20% and 43% of patients with Stage 1 and Stage 2 AKI, respectively, required a recovery time greater than 3 days (Figure 2). The patient who required dialysis recovered after approximately 3 weeks.

Of the 57 eligible patients, 46% were female and 54% were male. The median age of the cohort was 7 years (range 8 months to 20 years old.) There was no statistically significant difference between groups with regards to sex, Hispanic vs. non-Hispanic ethnicity, or elevated BMI (Table 3). The AKI group was older with a median age of 10 years as compared to 4 years ($p < 0.001$). The majority of patients with AKI (81%) were admitted to the pediatric Intensive Care Unit (ICU).

Within the AKI group with a documented urinalysis, we found that 44% had significant proteinuria ≥ 2+ (100 mg/dl), but there was no significant difference in proteinuria between those with AKI and those without ($p=0.58$). Half of the patients with AKI (13/26) had an abdominal and/or renal sonogram, of which only one sonogram revealed renal abnormalities with increased cortical echogenicity. Additional risk factors for AKI were evaluated: nephrotoxin exposure prior to AKI was identified in 54% of cases, and 69% of AKI patients required vasopressor support (Table 4). All patients who required fluid resuscitation received normal saline crystalloid boluses in accordance with pediatric life support guidelines (13, 14).

Patients with AKI were more likely to have left ventricular systolic dysfunction ($p < 0.001$). Peak inflammatory markers, including interleuken-6 (IL-6), ferritin, fibrinogen, D-dimer, Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), procalcitonin, as well as lymphopenia, defined as having an absolute lymphocyte count < 1500/$mm^3$ or < 2000/ $mm^3$ in children fewer than 6 years

of age (15), were compared between the two groups (Table 3). We found a statistically significant difference between the AKI and non-AKI groups when comparing peak inflammatory markers of CRP ($p < 0.01$), IL-6 ($p < 0.05$), procalcitonin ($p < 0.05$), and ferritin ($p < 0.001$). Similar to adult patients with AKI due to primary COVID-19 infection (16), lymphopenia occurred in MIS-C patients and occurred more often in the AKI group ($p <0.01$). Fibrinogen, D-dimer, LDH, and ESR were not significantly different across groups.

**Discussion**

Although AKI has been reported as a prominent feature in primary COVID-19 infection (6, 7, 10, 16-18), there has been limited studies describing AKI in MIS-C (2, 3, 9). To our knowledge, we present the first study to describe the characteristics of AKI in pediatric patients with MIS-C. We showed that, similar to adult patients with primary COVID-19 infection (7), AKI in MIS-C occurred early in hospitalization, with 97% of AKI occurring within 72 hours of admission. Importantly, resolution of AKI usually occurred rapidly, with 61% recovering within 3 days. The majority of cases were mild, KDIGO stage 1 AKI. More severe AKI took longer to resolve, but only one patient required dialysis (Figure 2). This swift improvement of AKI with medical management is in stark contrast to the clinical course of AKI from primary COVID-19 infection; need for renal replacement therapy has been reported at 55% and incidence of mortality at 50% in adult AKI patients with primary COVID-19 infection (6).

A limitation of our study is that we were unable to include values in analysis that occurred outside our laboratory's reference range, and therefore may have skewed significance. For example, the lowest creatinine value measured by our lab is < 0.2 mg/dL, but a value of 0.2 mg/dL was used for these patients. Likewise, several patients

had IL-6 levels > 315 pg/ml, but were analyzed using a value of 315 pg/mL. This limitation may have overestimated baseline creatinine and therefore underestimated AKI incidence, as well as blunted significance in inflammation between the AKI and non-AKI groups.

Given lack of previous laboratory values for most children, hospitalization nadir was treated as patients' baseline creatinine. However, unlike some adult patients with AKI in primary COVID-19 infection (6), none of the patients in our study had documented chronic kidney disease prior to hospitalization. The predominance of mild AKI in MIS-C with rapid recovery of renal function suggests transient hypo-perfusion, ischemia, or hypoxia. While the presenting symptoms of patients with MIS-C varied, they all included persistent fever by clinical definition. This, along with vomiting in some patients, may have contributed to dehydration. Additionally, most patients required ICU admission mostly due to hypotension with 69% requiring vasopressor support. A majority of patients with AKI (58%) had decreased left ventricular systolic function at time of AKI, another factor contributing to decreased effective renal perfusion. While the majority of AKI patients followed a clinical course most consistent with pre-renal injury, other etiologies of AKI, such as nephrotoxin exposure and acute tubular necrosis, might have contributed as well. This does underscore the importance of long-term follow up to ensure adequate renal function as these children grow into the adulthood.

The pathogenesis of AKI in children with MIS-C, which is considered a post-viral inflammatory response, is not clearly understood at the present time. Our data indicate that patients with MIS-C with AKI have a greater degree of inflammation compared to those who did not. These findings raise the concern whether inflammation- and cytokine-mediated hypotension lead to renal hypo-perfusion, as other systemic

inflammation, such as sepsis, has been associated with AKI (19). It is unknown whether intra-renal inflammation was present and contributed to AKI, since none of our patients underwent a renal biopsy, either due to lack of indication or clinically unstable to undergo biopsy. To treat the inflammatory condition, all MIS-C patients with AKI received steroids and 81% of them also received intravenous immunoglobulin (IVIG) for Kawasaki-like features. Nineteen percent of patients who had AKI were also given anakinra as a third-line agent. Effective anti-inflammatory treatment may facilitate prompt renal recovery.

Previous studies have reported younger age as a risk factor for pediatric multiple organ dysfunction syndrome (MODS), likely owing to the difference in physiology between neonates and older children (20, 21). No neonates were included in our population, with the youngest infant being 8 months of age, and the median age of our cohort was 7 years old. Our study found that the median age for children with AKI was significantly older than that of children without AKI during MIS-C. It is possible that younger children may have been brought to medical attention sooner than those of older age, allowing for timely medical interventions that prevented or reduced renal injury and facilitated renal recovery. Since our study only includes children who presented to the emergency department and/or were hospitalized, and none in ambulatory settings, older children with mild signs and symptoms resembling MIS-C may have been under-represented.

MIS-C is a new disease entity and we captured 58 children with the diagnosis during a six month period, including the height of the pandemic in New York. The relatively small sample size did not permit statistical analysis designed for data of normal distribution. Additionally, the sequence between clinical presentation and

laboratory finding with the occurrence and resolution of AKI was not examined. For example, only peak but not the trend of inflammatory markers was recorded, and timing of administering fluid, vasopressors and immunomodulatory agents as related to AKI was not studied. However, we did observe that shock and AKI usually occurred early in the hospitalization, which supports renal hypo-perfusion as a major contributing factor in causing AKI.

In conclusion, we were able to characterize AKI as it occurs in MIS-C and highlight substantial differences between AKI associated with MIS-C versus those with primary COVID-19 infection. We found that AKI was a common finding among pediatric patients hospitalized with MIS-C, with a significant difference in age and inflammatory markers, as well as cardiac function, between the MIS-C groups with and without AKI. AKI appears to be mild and has a short recovery period, which differs from AKI from primary COVID-19 infection. However, we have only had short follow-up since the resolution of AKI. Further clinical and translational studies are required to have a more complete understanding of this novel medical condition that involves multiple organs in children.

**Disclosures:**

I. Batal reports Research Funding: American Society of Transplantation outside the current work. F. Lin reports Honoraria: lectures and seminars in academic institutions; Scientific Advisor or Membership: JASN editorial board. All remaining authors have nothing to disclose.

**Funding:**

None

**Author Contributions:**

M Lipton: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review and editing

R G Mahajan: Conceptualization; Data curation; Investigation; Methodology; Writing - original draft

C Kavanagh: Data curation; Formal analysis; Methodology; Writing - original draft; Writing - review and editing

C Shen: Data curation; Writing - original draft

I Batal: Formal analysis; Methodology

S Dogra: Writing - review and editing

N Jain: Writing - review and editing

F Lin: Conceptualization; Investigation; Supervision; Writing - original draft; Writing - review and editing

N Uy: Conceptualization; Investigation; Methodology; Supervision; Writing - original draft; Writing - review and editing

## References:


1. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19, Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. Accessed December 16, 2020
2. Centers for Disease Control and Prevention: Multisystem Inflammatory Syndrome (MIS-C): Health Department -- Reported Cases of Multisystem Inflammatory Syndrome (MIS-C) in the United States, Available at: https://www.cdc.gov/mis-c/cases/index.html. Accessed December 16, 2020
3. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, Milner JD: Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. *JAMA* **324:** 294-296, 2020 10.1001/jama.2020.10374
4. Chiotos K, Bassiri H, Behrens EM, Blatz AM, Chang J, Diorio C, Fitzgerald JC, Topjian A, John ARO: Multisystem Inflammatory Syndrome in Children During the Coronavirus 2019 Pandemic: A Case Series. *Journal of the Pediatric Infectious Diseases Society* **9:** 393-398, 2020 10.1093/jpids/piaa069
5. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, Auriau J, Grimaud M, Oualha M, Beghetti M, Wacker J, Ovaert C, Hascoet S, Selegny M, Malekzadeh-Milani S, Maltret A, Bosser G, Giroux N, Bonnemains L, Bordet J, Filippo SD, Mauran P, Falcon-Eicher S, Thambo J-B, Lefort B, Moceri P, Houyel L, Renolleau S, Bonnet D: Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. *Circulation* **142:** 429-436, 2020 doi:10.1161/CIRCULATIONAHA.120.048360
6. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, Alqudsi M, LeDoux JR, Velez JCQ: Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. *Kidney360* **1:** 614-622, 2020 10.34067/kid.0002652020
7. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD: Acute kidney injury in patients hospitalized with COVID-19. *Kidney Int* **98:** 209-218, 2020 10.1016/j.kint.2020.05.006
8. Bjornstad EC, Krallman KA, Askenazi D, Zappitelli M, Goldstein SL, Basu RK: Preliminary Assessment of Acute Kidney Injury in Critically Ill Children Associated with SARS-CoV-2 Infection. *A Multicenter Cross-Sectional Analysis***:** CJN.11470720, 2020 10.2215/cjn.11470720
9. Capone CA, Subramony A, Sweberg T, Schneider J, Shah S, Rubin L, Schleien C, Epstein S, Johnson JC, Kessel A, Misra N, Mitchell E, Palumbo N, Rajan S, Rocker J, Williamson K, Davidson KW: Characteristics, Cardiac Involvement, and Outcomes of Multisystem Inflammatory Syndrome of Childhood Associated with severe acute respiratory syndrome coronavirus 2 Infection. *J Pediatr* **224:** 141-145, 2020 10.1016/j.jpeds.2020.06.044
10. Lipton M, Kavanagh CR, Mahajan R, Jain NG, Uy NS, Dogra S, Lin F: Role of pediatric nephrologists in managing adults with AKI due to COVID-19. *Pediatr Nephrol* **35**: 2019-2022, 2020 10.1007/s00467-020-04680-7
11. Outcomes KDIG: Summary of Recommendation Statements. *Kidney Int Suppl (2011)* **2:** 8-12, 2012 10.1038/kisup.2012.7
12. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL: AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol* **10:** 554-561, 2015 10.2215/cjn.01900214
13. Boluyt N, Bollen CW, Bos AP, Kok JH, Offringa M: Fluid resuscitation in neonatal and pediatric hypovolemic shock: a Dutch Pediatric Society evidence-based clinical practice guideline. *Intensive Care Medicine* **32:** 995-1003, 2006 10.1007/s00134-006-0188-4
14. Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, Berg MD, de Caen AR, Fink EL, Freid EB, Hickey RW, Marino BS, Nadkarni VM, Proctor LT, Qureshi FA, Sartorelli K,

Topjian A, van der Jagt EW, Zaritsky AL: Part 14: pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* **122:** S876-908, 2010 10.1161/circulationaha.110.971101

15. Long SS, Vodzak J: 288 - Laboratory Manifestations of Infectious Diseases. In: *Principles and Practice of Pediatric Infectious Diseases (Fifth Edition).* edited by Long SS, Prober CG, Fischer M, Elsevier, 2018, pp 1447-1459.e1444
16. Cheng Y, Luo R, Wang X, Wang K, Zhang N, Zhang M, Wang Z, Dong L, Li J, Zeng R, Yao Y, Ge S, Xu G: The Incidence, Risk Factors, and Prognosis of Acute Kidney Injury in Adult Patients with Coronavirus Disease 2019. *Clinical Journal of the American Society of Nephrology* **15:** 1394-1402, 2020 10.2215/cjn.04650420
17. Division of Nephrology CUVCoP: Disaster Response to the COVID-19 Pandemic for Patients with Kidney Disease in New York City. *J Am Soc Nephrol* **31:** 1371-1379, 2020 10.1681/ASN.2020040520
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* **395:** 1054-1062, 2020 10.1016/S0140-6736(20)30566-3
19. Powell TC, Powell SL, Allen BK, Griffin RL, Warnock DG, Wang HE: Association of inflammatory and endothelial cell activation biomarkers with acute kidney injury after sepsis. *Springerplus* **3:** 207, 2014 10.1186/2193-1801-3-207
20. Bestati N, Leteurtre S, Duhamel A, Proulx F, Grandbastien B, Lacroix J, Leclerc F: Differences in organ dysfunctions between neonates and older children: a prospective, observational, multicenter study. *Critical Care* **14:** R202, 2010 10.1186/cc9323
21. Watson RS, Crow SS, Hartman ME, Lacroix J, Odetola FO: Epidemiology and Outcomes of Pediatric Multiple Organ Dysfunction Syndrome. *Pediatr Crit Care Med* **18:** S4-S16, 2017 10.1097/PCC.0000000000001047

## Figure 1: Enrollment Criteria and SARS-COV-2 Testing

## Figure 2: Time to AKI Recovery By KDIGO Stage

## Table 1: CDC Criteria for MIS-C

## Table 2: KDIGO Classification

## Table 3: Demographics and Clinical Characteristics of MIS-C Patients

## Table 4: Clinical Characteristics of AKI Cohort

**Figure 1: Enrollment Criteria and SARS-CoV-2 Testing**

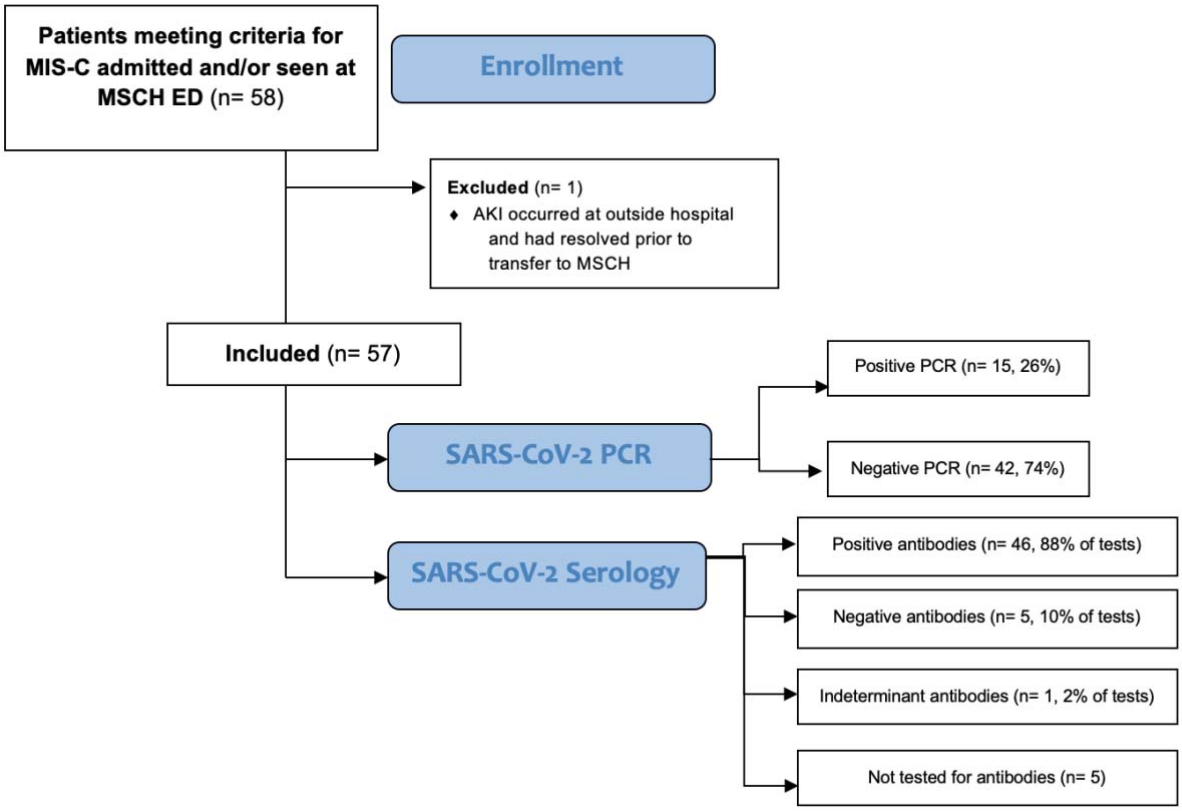


Figure 1.

CONSORT diagram outlining enrollment of cohort, who met criteria for Multisystem Inflammatory Syndrome in Children (MIS-C) and presented to Morgan Stanley Children's Hospital (MSCH), indicating SARS-CoV-2 testing, RT-PCR and serology

**Figure 2: Time to AKI Recovery, by KDIGO Stage**

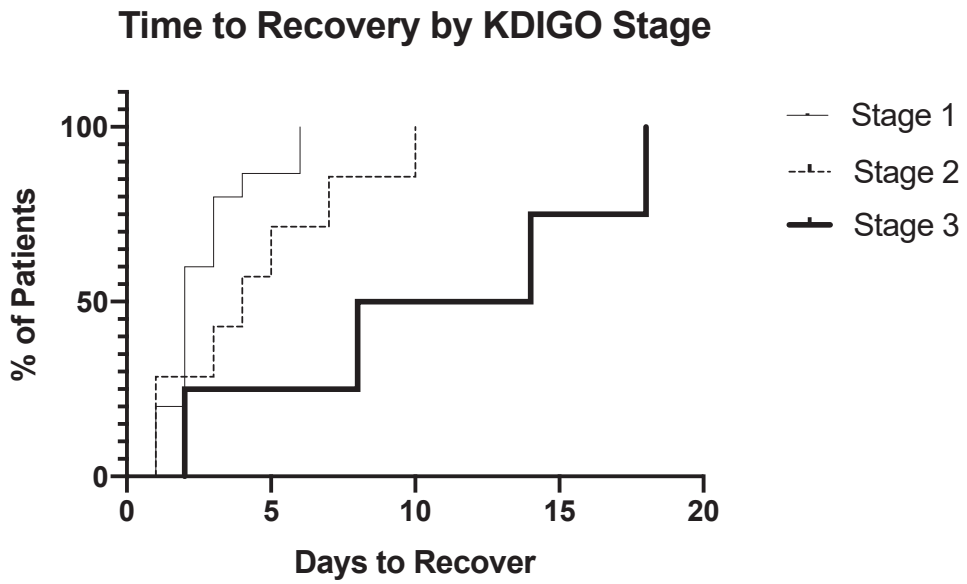


Figure 2.

Kaplan-Meir curve outlining time to recovery of Acute Kidney Injury (AKI) by Kidney Disease Improving Global Outcomes (KDIGO) Stage.

**Table 1: CDC criteria for MIS-C**

| |
|---|
| Age <21 years |
| Clinical presentation consistent with MIS-C, including **all** of the following: |
| Fever:<br>Documented fever >38.0°C (100.4°F) for ≥24 hours **OR**<br>Report of subjective fever lasting ≥24 hours |
| Laboratory evidence of inflammation<br>Including, but not limited to, **any** of the following:<br>▪ Elevated CRP<br>▪ Elevated ESR<br>▪ Elevated fibrinogen<br>▪ Elevated procalcitonin<br>▪ Elevated D-dimer<br>▪ Elevated ferritin<br>▪ Elevated LDH<br>▪ Elevated IL-6 level<br>▪ Neutrophilia<br>▪ Lymphocytopenia<br>▪ Hypoalbuminemia |
| Severe illness requiring hospitalization |
| Multisystem involvement<br>**2 or more** organ systems involved:<br>▪ Cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia)<br>▪ Respiratory (eg, pneumonia, ARDS, pulmonary embolism)<br>▪ Renal (eg, AKI, renal failure)<br>▪ Neurologic (eg, seizure, stroke, aseptic meningitis)<br>▪ Hematologic (eg, coagulopathy)<br>▪ Gastrointestinal (eg, elevated liver enzymes, diarrhea, ileus, gastrointestinal bleeding)<br>▪ Dermatologic (eg, erythroderma, mucositis, other rash) |
| No alternative plausible diagnoses |
| Recent or current SARS-CoV-2 infection or exposure |

**Table 2: KDIGO Classification**

| KDIGO Stage | Serum Creatinine |
|---|---|
| 1 | 1.5–1.9 times baseline OR 0.3 mg/dl increase |
| 2 | 2.0–2.9 times baseline |
| 3 | 3.0 times baseline OR<br>Increase in serum creatinine to 4.0 mg/dl OR<br>Initiation of renal replacement therapy OR<br>Decrease in eGFR to 35 ml/min per 1.73 $m^2$ (in patients over 18 yrs) |

**Table 3: Demographics and Clinical Characteristics of MIS-C Patients**

| | AKI (n=26) | Non- AKI (N=31) | p- value |
|---|---|---|---|
| **Age (Years)**<br>Median (Range) | 10 (2-20) | 4 (0-17) | 0.0004 |
| **Sex**<br>-Male<br>-Female | <br>14/26= 54%<br>12/26= 46% | <br>14/31= 45%<br>17/31= 55% | <br>0.5990 |
| **Hispanic Ethnicity** | 8/26= 31% | 9/31= 29% | 1.0000 |
| **BMI ≥ 85$^{th}$ %tile** | N=26<br>15/26= 58% | N=30<br>13/30=43% | 0.4218 |
| **LV Systolic Dysfunction** | N=26<br>15/26= 58% | N=28<br>2/28= 7% | 0.0001 |
| **Lymphopenia**<br>defined as <1500/mm$^3$ | 24/26= 92% | 18/31=26% | 0.0056 |
| **Interleukin-6 (pg/mL)**<br>Median (Range) | N=20<br>274.5 (32.0-315.0) | N=15<br>46.7 (3.0-315.0) | 0.0151 |
| **Peak Ferritin (ng/mL)**<br>Median (Range) | N= 26<br>670.5 (284-100,000) | N=29<br>233.1 (19.9-2769) | 0.00003 |
| **Peak Fibrinogen (mg/dL)**<br>Median (Range) | N=26<br>624 (166-875) | N=24<br>501.5(273-838) | 0.0988 |
| **Peak D-dimer (ug/mL FEU)**<br>Median (Range) | N=26<br>3.9 (0.5- 426) | N=28<br>2.9 (0.3-20.0) | 0.3541 |
| **Peak LDH (U/L)**<br>Median (Range) | N=25<br>339 (207-4087) | N=27<br>356 (178-1295) | 0.8047 |
| **Peak CRP (mg/L)**<br>Median (Range) | N=26<br>211 (29.4-300) | N=30<br>135.1 (0.21-300.0) | 0.0099 |
| **Peak ESR (mm/hr)**<br>Median (Range) | N=20<br>56.5 (23-130) | N=23<br>59.0 (0-130) | 0.9708 |
| **Peak Procalcitonin (ng/mL)**<br>Median (Range) | N=23<br>3.6 (0.2-126.9) | N= 24<br>1.6 (0.1-42.1) | 0.0171 |
| **Significant Proteinuria**<br>defined as ≥ 2+ on dipstick | N=25<br>11/25= 44% | N=29<br>10/29=34% | 0.5789 |

Patients for whom certain data were unavailable or missing were excluded from analysis regarding that factor. Lymphopenia is defined as having an absolute lymphocyte count < 1500/mm$^3$ (or < 2000/ mm$^3$ in children fewer than 6 years of age). AKI, Acute Kidney Injury; MIS-C, Multisystem Inflammatory Syndrome in Children; BMI, Body Mass Index; LV, Left Ventricular; LDH, lactate dehydrogenase; CRP, C-Reactive protein; ESR, Erythrocyte Sedimentation Rate

**Table 4: Clinical characteristics of AKI cohort**

| | **AKI**<br><br>(n = 26) |
|---|---|
| Bed location<br><br>ICU<br><br>General ward | <br><br>21 (81%)<br><br>5 (19%) |
| Nephrotoxic medications* | 14 (54%) |
| Decreased left ventricular systolic function | 15 (58%) |
| Vasopressors | 18 (70%) |
| Mechanical ventilation | 1 (4%) |
| Dialysis | 1 (4%) |
| Treatment<br><br>Steroids<br>IVIG<br>Anakinra | <br><br>26 (100%)<br>21 (81%)<br>5 (19%) |

AKI, Acute Kidney Injury; ICU, Intensive Care Unit; IVIG, intravenous immunoglobulin

*nephrotoxic medications include aminoglycosides, trimethoprim/sulfamethoxazole, vancomycin, acyclovir, nonsteroidal anti-inflammatory drugs (NSAIDs), iodine-based contrast for imaging, and calcineurin inhibitors