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Distinguishing Multisystem Inflammatory Syndrome in Children From Kawasaki Disease and Benign Inflammatory Illnesses in the SARS-CoV-2 Pandemic

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Abstract

Objective: The aim of the study was to compare presenting clinical and laboratory features among children meeting the surveillance definition for multisystem inflammatory syndrome in children (MIS-C) across a range of illness severities.

Methods: This is a retrospective single-center study of patients younger than 21 years presenting between March 1 and May 15, 2020. Included patients met the Centers for Disease Control and Prevention criteria for MIS-C (inflammation, fever, involvement of 2 organ systems, lack of alternative diagnoses). We defined 3 subgroups by clinical outcomes: (1) critical illness requiring intensive care interventions; (2) patients meeting Kawasaki disease (KD) criteria but not requiring critical care; and (3) mild illness not meeting either criteria. A comparator cohort included patients with KD at our institution during the same time frame in 2019.

Results: Thirty-three patients were included (5, critical; 8, 2020 KD; 20, mild). The median age for the critical group was 10.9 years (2.7 for 2020 KD; 6.0 for mild, $P = 0.033$). The critical group had lower median absolute lymphocyte count (850 vs 3005 vs 2940/uL, $P = 0.005$), platelets (150 vs 361 vs 252 k/uL, $P = 0.005$), and sodium (129 vs 136 vs 136 mmol/L, $P = 0.002$), and higher creatinine (0.7 vs 0.2 vs 0.3 mg/dL, $P = 0.002$). In the critical group, 60% required vasoactive

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medications, and 40% required mechanical ventilation. Clinical and laboratory features were similar between the 2020 and 2019 KD groups.

Conclusions: We describe 3 groups with inflammatory syndromes during the SARS-CoV-2 pandemic. The initial profile of lymphopenia, thrombocytopenia, hyponatremia, and abnormal creatinine may help distinguish critically ill MIS-C patients from classic/atypical KD or more benign acute inflammation.

Keywords

COVID-19; Kawasaki disease; multisystem inflammatory system in children (MIS-C); SARS-CoV-2

On April 25, 2020, the Pediatric Intensive Care Society of the United Kingdom released an alert regarding cases of a “multisystem inflammatory state” occurring in pediatric patients during the pandemic of coronavirus disease 2019. The first peer-reviewed case series was published in early May 2020,¹ and since then, hundreds of cases have been reported in the United States and Europe.^{2–6} The most consistent features of the syndrome include cardiovascular dysfunction, gastrointestinal symptoms, and variable conjunctivitis, rash, mucous membrane changes, and extremity swelling, elements shared with other hyperinflammatory states such as classic or atypical Kawasaki disease (KD). On May 14, 2020, the US Centers for Disease Control and Prevention (CDC) released a case definition for this syndrome, which it designated “multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019”: (1) fever of 38.0°C or greater for 24 hours or more; (2) laboratory evidence of inflammation; and (3) clinically severe illness requiring hospitalization involving 2 or more organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), with no alternative plausible diagnoses and evidence of SARS-CoV-2 exposure within 4 weeks.⁷

Many of the patients identified with this syndrome have been critically ill; however, the CDC surveillance definition and early multicenter reports suggest that there may be a broader spectrum of disease. To date, 3 studies (2 consisting of patients across centers in the United States, 1 describing cases in France) describe patients meeting MIS-C criteria who have clinical overlap with classic KD,^{3,4,7} but, to this point, there has yet to be a study identifying clinical and laboratory features that may help distinguish patients with MIS-C who go on to critically illness from those with classic KD or more benign inflammatory illnesses. Given the breadth of the definition of “severe illness” and the relatively low prevalence of disease, defining clinical and laboratory features that distinguish critically ill patients from those with lower severity is of paramount importance, particularly for providers in the emergency department (ED) setting who are conducting the initial evaluation of such patients.

The primary objective of this study was to compare clinical and laboratory features among pediatric patients meeting surveillance definition of MIS-C but presenting with a range of illness severity; we included patients presenting to the ED of a large, tertiary care children’s hospital in a region with widespread community transmission of SARS-CoV-2.

The secondary objective was to compare features of noncritically ill children meeting criteria for KD in 2020 to those treated for KD during a similar timeframe in 2019.

METHODS

Study Design and Setting

We performed a retrospective cohort study of patients younger than 21 years seen in the ED of our urban tertiary care free-standing children's hospital in southeastern Pennsylvania between March 1, 2020, and May 15, 2020. The first recorded case of SARS-CoV-2 in our region was March 7, 2020. To identify children with inflammation, we initially included all ED patients who were admitted to the hospital with an elevated erythrocyte sedimentation rate (ESR) of 40 mm/h or greater or C-reactive protein (CRP) of 3.0 mg/dL, consistent with consensus recommendations from the American Heart Association for inflammation in the setting of evaluation for incomplete KD.⁹ We then conducted manual medical record reviews to identify the subset of patients admitted to the hospital with fever and at least 2 organ systems involved, to align with the proposed CDC definition for MIS-C. We then excluded patients without fever, with less than 2 organ systems involvement, and in whom an alternative diagnosis explained the elevation in inflammatory markers. We determined presence of an alternative diagnosis by agreement of 2 authors (D.C. and F.B.), and any discrepancies were resolved by a third author (L.S.). Given the widespread community prevalence of SARS-CoV-2 in our region, and inconsistent documentation of exposure history in the early days of the pandemic, we did not use documented exposure as an inclusion criterion. Of note, a portion of critically ill patients with MIS-C included in this cohort were included in prior studies, including an initial cases series at our institution (3 patients),² a description of cytokine panel differences between those with severe coronavirus disease 2019 and those with MIS-C (2 patients),¹⁰ and a large, multicenter cohort of MIS-C patients across the United States (4 patients).⁴ As a secondary analysis, we included a comparator cohort of all children who were treated for KD at our institution from March 1 to May 15, 2019. The study was determined to be exempt from institutional board review by our institution's institutional board review.

Data Collection

We collected the following data elements by medical record review: demographics; medical history (including, but not limited to, asthma, chronic lung disease, congenital heart disease, inflammatory bowel disease, cerebral palsy, epilepsy, sickle cell disease, autoimmune disorder, immunologic disorders, or oncologic diagnoses); history of presentation (including fever duration and symptomatology); initial physical examination findings; initial and most extreme laboratory results at our institution; imaging results (including echocardiogram results, with coronary artery dilation defined as a Z score ≥ 2.5)⁹; medications administered; intensive care interventions (including vasoactive medication administration, and either noninvasive or invasive ventilation), and hospital length of stay. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools.

Data Analysis

We categorized patients into three subgroups for analysis: (1) patients with critical illness, defined as patients admitted to the intensive care unit at our institution and requiring critical care interventions, including vasoactive support, mechanical ventilation, or noninvasive positive pressure ventilation (“critical illness”); (2) patients meeting criteria for either classic or incomplete KD during the course of hospitalization, but not requiring critical care interventions (“2020 KD”); and (3) patients with mild illness not meeting KD criteria and not requiring critical care interventions (“mild illness”). The American Heart Association definitions were used to classify patients as either classic or incomplete KD.⁹ We compared proportions using χ^2 or Fisher exact test, where appropriate. Given the nonparametric distribution of our data, for continuous variables, we reported medians and interquartile ranges (IQRs), and compared distributions using either Kruskal-Wallis or Wilcoxon rank sum test. For our secondary analysis, we compared noncritically ill patients with KD in 2020 with patients who received intravenous immunoglobulin for KD at our institution over the same time period in 2019. All analyses were conducted using Stata Version 14.2 (StataCorp, College Station, Tex).

RESULTS

We identified 228 patients in the 2020 period with elevated inflammatory markers. These, ultimately, included 33 patients in our sample who met the CDC MIS-C surveillance definition. Reasons for exclusion, including the most common alternative diagnoses, are shown as a flow diagram in Figure 1, Supplemental Digital Content, <http://links.lww.com/PEC/A627>. Of the 33 included patients, 5 were in the “critical illness” group, 8 in “2020 KD” group, and 20 in the “mild illness” group. Demographics, historical features, and physical examination findings are presented in Table 1, Supplemental Digital Content, <http://links.lww.com/PEC/A628>. Those in the critical illness group were older (median [IQR], 10.9 years [9.3–13.8]) compared with the other groups (2.7 [1.5–4.3] in the 2020 KD group, 6.0 [1.9–14.7] in the mild illness group, $P = 0.033$). Patients in the 2020 KD group were more likely to report a history of conjunctival injection (87.5% vs 40% in the critical illness group vs 10% in the mild illness group, $P < 0.001$), history of a rash (75% vs 40% and 20%, respectively, $P = 0.017$), or history of extremity changes (75% vs 20% and 15%, respectively, $P = 0.007$). Diarrhea was more common in the critical illness group (100% vs 62.5% in 2020 KD group vs 10% in the mild illness group, $P < 0.001$). In total, 2 patients in the critical illness group met criteria for KD (both incomplete disease). Four of the patients in the 2020 KD group met criteria for classic disease, whereas the other 4 met criteria for incomplete KD.

In comparing initial laboratory values (Table 1), those in the critical illness group had lower median (IQR) absolute lymphocyte (ALC) counts (850 [300–910] vs 3005 [1710–3510] and 2940/uL [1605–4725], $P = 0.005$) and median (IQR) platelet counts (150 [135–155] vs 361 [317–461] vs 252 k/uL [204–492], $P = 0.005$) compared with the moderate and mild illness groups, respectively. The median (IQR) initial sodium (129 [125–129] vs 136 [134–137] vs 136 mmol/L [135–140], $P = 0.002$) and creatinine (0.7 [0.6–1.5] vs 0.2 [0.2–0.3] vs 0.3 mg/dL [0.2–0.5], $P = 0.002$) were also significantly different between the groups. When

evaluating the following combination of values: ALC of less than 1000/uL, platelet count of less than 150 k/uL, sodium of less than 135 mg/dL, and creatinine abnormal for age, we found 4 of 5 critical illness patients had at least 3 of these features (all had at least 2 features); comparatively, all 8 patients in the 2020 KD group and 19 of 20 patients in the mild illness group had 0 or 1 of these values present (Table 2). Laboratory differences between groups were even more pronounced when comparing most extreme values during the course of hospitalization, particularly in regards to maximum white blood cell count and absolute neutrophil count, and minimum ALC and hemoglobin (Table 2, Supplemental Digital Content, <http://links.lww.com/PEC/A630>).

SARS-CoV-2 polymerase chain reaction (PCR) was positive in 5 of 9 critically ill patients, and SARS-CoV-2 immunoglobulin G (IgG) antibodies were positive in all 5 critically ill patients tested (including 3 of the 4 who were negative by PCR). SARS-CoV-2 antibodies were obtained in 2 of 10 patients in the moderate illness and 2 of 20 patients in the mild illness groups, all of which were negative.

For the 18 patients who had echocardiograms (Table 1), only patients in the critically ill group had ventricular dysfunction (66.7% vs 0% vs 0%, $P < 0.001$). Three of the 5 critically ill patients required vasoactive medications, and all 5 required either mechanical ventilation or noninvasive positive pressure ventilation. All patients in the critical illness and the 2020 KD groups received intravenous immunoglobulin. The median hospital length of stay (IQR) was 10 days (8–11) in the critical illness versus 5 (4–7) in the 2020 KD versus 2 (2–4) in the mild illness group ($P = 0.003$), and there were no patient deaths. One patient in the cohort (a patient in the 2020 KD group returning with persistent fever, who did not receive any additional treatment) returned to our institution within 72 hours of discharge. In the mild illness group, 1 patient returned with 2 weeks of discharge because of dehydration secondary for dehydration.

In comparing the cohort of patients meeting criteria for KD but not requiring critical care interventions in 2020 with the 2019 KD patients at our institution (15 total patients in 2019, 9 with classic KD, 6 with incomplete KD), there were no differences in median age, sex, incidence of each individual KD stigmata, or laboratory features, including most extreme white blood cell count (WBC), ALC, platelet count, sodium, creatinine, ESR, or CRP (Table 3, Supplemental Digital Content, <http://links.lww.com/PEC/A629>). Four of the 15 patients received viral testing in the 2019 cohort, 3 of which were positive for non-SARS-CoV-2 coronaviruses.

DISCUSSION

In evaluating a cohort of children admitted to our institution with laboratory evidence of inflammation during the SARS-CoV-2 pandemic, we identified 3 subsets of patients: those requiring critical care interventions, those meeting diagnostic criteria for either classic or atypical KD but not requiring critical care, and those with mild illness who recovered without critical care intervention. We found that absolute lymphocyte count, platelet count, serum sodium, and serum creatinine obtained upon ED presentation were helpful in discriminating between the critically ill and less severely ill patients.

Our critical illness group had many features comparable with large case series of MIS-C, including age ranges, laboratory features, signs of cardiac dysfunction, and treatment outcomes,^{3–6} similarities that have been described in detail in the case series by Chiotos et al.² In an attempt to better understand potential differences between these critically ill children, and children presenting with inflammation without requiring critical care interventions, we further classified hospitalized children into 2 additional groups: those meeting criteria for either classic or incomplete KD and those with mild, undifferentiated inflammation.

Nearly two thirds of the patients in our cohort who met CDC criteria for MIS-C (absent a known exposure) fell into the category of a mild inflammatory illness. We hypothesize that this group is polymorphic and likely includes children with unspecified viral infections, potentially a milder form of MIS-C, or some combination of both. The laboratory profile of these patients was particularly distinct from those with critical illness. In this small series, these children were unlikely to have lymphopenia, thrombocytopenia, hyponatremia, or abnormal creatinine for age (of these 4 features, only 0 or 1 were present in 19/20 of the patients in the mild illness group; the only patient with >1 feature was an oncology patient, whose laboratory results were at baseline). Of note, these laboratory features are not specific for MIS-C and may instead be more broadly representative of critical illness. Previous studies have evaluated the incidence of lymphopenia, thrombocytopenia, and hyponatremia in critically ill children and found associations between critical illness and these laboratory findings.^{11–13} In particular, a prognostic association has been shown between hyponatremia and morbidity.¹⁴ Regardless of the underlying etiology, all of our mild illness patients were able to be discharged home with minimal interventions (after a median 2-day hospital admission), without any return visits within 72 hours of discharge, and only 1 with a subsequent visit within 2 weeks (for dehydration unrelated to inflammation). This suggests that in the ED setting, patients who have abnormal inflammatory markers alone (regardless of etiology) may be identified for monitoring as outpatients without requiring hospital admission. Future studies to determine whether these laboratory findings are useful in ruling out MIS-C are warranted.

Our cohort of noncritically ill patients who met criteria for KD in 2020 displayed significant similarities in clinical presentation, examination findings, and laboratory values to patients who were diagnosed with KD over the same timeframe in 2019. The clinical histories and laboratory findings of both groups are also consistent with larger case series of KD¹⁵ and markedly different from the critically ill children with likely MIS-C in this sample. Whittaker et al,¹⁶ Verdoni et al,¹⁷ and Lee et al¹⁸ compared their cases of MIS-C in England, Italy, and Boston, respectively, with historical cases of KD, and found similar distinctions, particularly with regard to age, lymphocyte counts, platelet counts, and sodium level. Other large, multicenter studies in the United States and Europe have alluded to a possible distinction between MIS-C and KD. In the 2 largest US studies of MIS-C to date, in New York by Dufort et al³ (95 patients), and across the United States by Feldstein et al⁴ (186 patients), patients younger than 5 years were more likely to present with KD features than older children, and in the New York cohort, less likely to require intensive care or show evidence of myocarditis. In a study of 156 cases reported to a French national surveillance system for suspicion of MIS-C by Belot et al,⁸ 25% of reported cases

were ultimately attributed to KD, rather than MIS-C. Although laboratory values are not reported in this brief surveillance data, median ages for both their MIS-C and KD cases were quite similar to our cohort (medians of 8.0 and 3.0 years in their study, respectively, as opposed to 10.9 and 2.7 years in ours). Taken together, these data suggest that non-SARS-CoV-2-mediated “true” KD likely continues to occur in the mid of the SARS-CoV-2 pandemic, although we cannot determine from our observations the relationship of these patients to SARS-CoV-2 infections (of the 7 patients tested in our 2020 KD group, only 1 was positive for SARS-CoV-2 by PCR, and of the 2 patients tested for SARS-CoV-2, antibodies in this group neither were positive). Although the underlying pathophysiology of KD and its overlap with MIS-C remains unknown, it is postulated to involve a dysregulated immune response, possibly secondary to a viral trigger. Interestingly, studies evaluating the prevalence of respiratory viruses in KD patients have shown some correlation with non-COVID-19 coronaviruses,¹⁹ and in our 2019 cohort of KD patients, 3 patients were positive for non-SARS-CoV-2 coronaviruses. Although serologic testing can establish prior exposure to SARS-CoV-2, use of this test to establish a MIS-C diagnosis may be challenging given the imperfect performance characteristics of some assays and possible prolonged seropositivity, such that a positive test may indicate a remote infection unrelated to the current hyperinflammatory state.

There are several limitations to our study. As this study was conducted in a single center, our results may not be applicable to a broader population of patients with possible MIS-C. As we relied on laboratory evidence of inflammation for inclusion into our sample, it is possible that there were patients who presented during this time with systemic inflammation on whom laboratory testing was not obtained. The retrospective nature of our study limited our ability to report comprehensive laboratory findings, including SARS-CoV-2 serologies, for all subjects, as well as ascertain true exposure status to SARS-CoV-2 infection in patients ultimately included in the sample. However, challenges in determining SARS-CoV-2 exposure or previous asymptomatic infection, particularly early in the course of clinical illness, reflect the real-world challenge faced by providers. In highly endemic areas, SARS-CoV-2 infection may in practice be presumed without known exposure, as was assumed in our study.

In conclusion, this study characterizes the clinical and laboratory features of children hospitalized with nonspecific inflammation during the SARS-CoV-2 pandemic and suggests the presence of 3 distinct groups: those with severe MIS-C requiring critical care, those with “usual features” of KD, and those with a mild inflammatory illness. The profile of lymphopenia, thrombocytopenia, hyponatremia, and abnormal creatinine patients upon presentation may help distinguish patients who will develop critical illness from those with usual KD or more benign acute infectious inflammation. Further research is needed to determine the diagnostic and prognostic value of this constellation of findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.
Initial Laboratory Results at Our Institution, Echocardiogram Results, Respiratory Support, and Length of Stay

	Reference Range	Critical Illness (n = 5)	Moderate Illness (n = 8)	Mild Illness (n = 20)	P
Median (IQR) initial WBC, k/uL	4.3–11.0	14.2 (11.7–16.0)	12.3 (9.4–17.9)	11.7 (10.4–14.5)	0.703
Median (IQR) initial ANC, /uL	1540–7920	12,260 (11,140–14,070)	7405 (6250–11,305)	6710 (5130–9470)	0.052
Median (IQR) initial ALC, /uL	970–3960	850 (300–910)	3005 (1710–3510)	2940 (1605–4725)	0.005
Median (IQR) initial hemoglobin, g/dL	11.5–15.5	12.4 (11.2–12.5)	10.6 (10.0–11.5)	11.3 (10.7–12.6)	0.254
Median (IQR) initial platelet count, k/uL	150–400	150 (135–155)	361 (317–461)	252 (204–492)	0.005
Median (IQR) initial sodium, mmol/L	138–145	129 (125–129)	136 (134–137)	136 (135–140)	0.002
Median (IQR) initial albumin, g/dL	3.7–5.6	3.8 (3.6–4.0)	4.4 (3.6–4.4)	4.3 (3.9–4.6) (n = 18/20)	0.174
Median (IQR) initial creatinine, mg/dL	0.1–1.0, age dependent	0.7 (0.6–1.5)	0.2 (0.2–0.3)	0.3 (0.2–0.5)	0.002
Median (IQR) initial ESR, mm/h	0–20	58 (38–90) (n = 4/5)	76 (49–88)	52 (33–90) (n = 16/20)	0.698
Median (IQR) initial CRP, mg/dL	0.0–0.9	16.8 (14.7–23.5)	6.7 (3.0–11.4)	7.2 (4.5–15.1)	0.090
Median (IQR) initial procalcitonin, ng/mL	0.00–0.10	15.2 (14.2–15.3) (n = 3/5)	1.4 (1.4–1.4) (n = 1/8)	12.4 (0.2–24.7) (n = 2/20)	0.465
Median (IQR) initial BNP, pg/mL	0.0–100.0	664 (562–818) (n = 4/5)	163 (10–234) (n = 3/8)	15 (10–25) (n = 4/20)	0.025
Median (IQR) initial troponin, ng/mL	0.00–0.30	0.48 (0.21–0.99) (n = 4/5)	(0.01–0.01) (n = 3/8)	(0.01–0.02) (n = 6/20)	0.009
Median (IQR) initial D-dimer, ug/mL	0.00–0.499	3.6 (1.8–5.7) (n = 4/5)	1.9 (1.6–2.2) (n = 2/8)	0.7 (0.5–0.8) (n = 4/20)	0.032
Positive SARS-CoV-2 PCR, n/tested (%)		3/5 (60.0)	1/7 (14.3)	1/14 (7.1)	0.049
Positive SARS-CoV-2 IgG, n/tested (%)		2/2 (100)	0/2 (0)	0/2 (0)	0.200
Positive SARS-CoV-2 PCR OR IgG, n/tested (%)		4/5 (80.0)	1/7 (14.3)	1/14 (7.1)	0.003
Abnormal ventricular function on echo, n/tested (%)		3/5 (60.0)	0/8 (0)	0/5 (0)	0.009
Coronary artery dilation on echo, n/tested (%)		2/5 (60.0)	0/8 (0)	0/5 (0)	0.054
Vasoactive medications administered, n (%)		3 (60.0)	0 (0)	0 (0)	0.002
Intravenous immunoglobulin administered, n (%)		5 (100)	8 (100)	0 (0)	<0.001
Corticosteroids administered, n (%)		5 (100)	3 (37.5)	1 (5.0)	0.001
NIPPV administered, n (%)		3 (60.0)	0 (0)	0 (0)	<0.001
Intubation, n (%)		2 (40.0)	0 (0)	0 (0)	0.019
Median (IQR) hospital length of stay in days		10 (8–11)	5 (4–7)	2 (2–4)	0.003

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Laboratory values reported collected on all patients unless otherwise noted.

ANC indicates absolute neutrophil count; BNP, brain natriuretic peptide; IVIG, intravenous immunoglobulin; NIPPV, noninvasive positive pressure ventilation.

TABLE 2.

Proportion of Abnormal Absolute Lymphocyte Count, Platelet Count, Sodium, and Creatinine by Group and Cumulative Number of Abnormal Values

	Critical Illness (n = 5)	2020 KD (n = 8)	Mild Illness (n = 20)	P
ALC <1000 u/L, n (%)	4 (80.0)	0 (0.0)	1 (5.0)	0.001
Platelet <150 k/uL, n (%)	2 (40.0)	0 (0.0)	1 (5.0)	0.089
Sodium <135 mmol/L, n (%)	5 (100)	3 (37.5)	4 (20.0)	0.003
Abnormal creatinine for age, n (%)	3 (60.0)	0 (0.0)	0 (0)	0.002
Cumulative no. abnormal elements (ALC, platelet, sodium, creatinine)				<0.001
0	0 (0)	5 (62.5)	16 (80.0)	
1	0 (0)	3 (37.5)	3 (15.0)	
2	1 (20.0)	0 (0)	0 (0)	
3	4 (80.0)	0 (0)	1 (5.0)*	
4	0 (0)	0 (0)	0 (0)	

* Patient with underlying oncologic disorder, whose lymphocyte count, platelet count, and sodium were all at baseline.