RESEARCH PAPER

Factors Differentiating Multisystem Inflammatory Syndrome in Children (MIS-C) From Severe/Critical COVID-19 Infection in Children

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Objective: To differentiate severe/critical coronavirus disease 2019 (COVID-19) infection from multisystem inflammatory syndrome in children (MIS-C). **Methods:** Single-center chart review comparing characteristics of children with MIS-C and 'severe/critical' COVID-19 infection. Multivariate logistic regression was performed to create predictive models for predicting MIS-C. **Results:** Of 68 patients, 28 (41.2%) had MIS-C while 40 (58.8%) had severe/critical COVID-19 infection. MIS-C patients had a higher prevalence of fever, mucocutaneous, cardiac and gastrointestinal involvement and a lower prevalence of respiratory symptoms (P<0.05). Significantly lower hemoglobin, platelet count, serum electrolytes, and significantly elevated inflammatory and coagulation markers were observed in MIS-C cohort. Upon multivariate logistic regression, the best model included C-reactive protein (CRP), platelet count, gastrointestinal and mucocutaneus involvement and absence of respiratory involvement (performance of 0.94). CRP>40 mg/L with either platelet count <150x10^9 or mucocutaneous involvement had specificity of 97.5% to diagnose MIS-C. **Conclusion:** Elevated CRP, thrombocytopenia and mucocutaneous involvement at presentation are helpful in differentiating MIS-C from severe COVID-19.

Keywords: *C-reactive protein, Comorbidity, Platelet count*, SARS-CoV-2.

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Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a spectrum of disease in children ranging from asymptomatic patients to critical coronavirus disease 2019 (COVID-19) requiring admission to the pediatric intensive care unit (PICU) [1]. It can also present with multisystem involvement including with circulatory shock and systemic inflammation, called as multisystem inflammatory syndrome in children (MIS-C) [2].

Patients with severe and critical COVID-19 infection (SC-COVID-19) and MIS-C present with non-specific symptoms, which often overlap, and differentiating these on presentation becomes difficult. Studies comparing the presenting symptoms and laboratory findings among these conditions are lacking. A recent systematic review showed that patients with MIS-C may have higher prevalence of gastrointestinal (GI), dermatologic and cardiovascular symptoms; however, this review included studies with significant heterogeneity in their inclusion criteria [4]. Similarly, hypoxemia, mechanical ventilation and use of inotropic drugs are more likely to occur in children with MIS-C [5]. Given the differences in treatment options, differentiating these two conditions at presentation is critical. In this study, we aimed to identify the clinical characteristics and laboratory markers at presentation that could help differentiate SC-COVID-19 in children from MIS-C.

METHODS

This is a retrospective chart review of children admitted to Oklahoma Children's Hospital from April 1- Dec 31, 2020 with diagnoses of MIS-C or SC-COVID-19. This study was approved by our institutional review board. We included data of patients aged 0-21 years with a diagnosis of SC-COVID-19 or MIS-C. Patients with no anthropometric data upon admission were excluded. Case definition of severe COVID-19 included individuals who had SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%, while critical COVID-19 included individuals who had respiratory failure, septic shock, and/or multiple organ dysfunction [6] . The case definition of MIS-C included an individual aged <21 years presenting with fever (≥38.0°C for ≥24 hours), laboratory evidence of inflammation (including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen,

procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, GI, dermatologic or neurological); and no alternative plausible diagnoses; and positive for current or recent SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms [3].

Data were collected by a review of electronic medical records. Demographics included age, gender and race. Clinical data included nutritional status, presence of comorbidities, symptoms at presentation, systems involved, presence of coinfections, need for PICU admission, oxygen requirement and maximum level of oxygen support required (none, nasal cannula, positive airway pressure (PAP), invasive mechanical ventilation), hospital length of stay (LOS), inotrope use and mortality. Nutritional status was classified based on current American Academy of Pediatrics guidelines into underweight (weight-for-length <2nd percentile or body mass index (BMI) <5th percentile), normal weight (weight for length 2nd-98th percentile or BMI 5th-85th percentile) and overweight/obese (weight for length ≥98th percentile or BMI ≥85th percentile) [7,8]. Laboratory markers obtained at presentation included white blood cell count, hemoglobin, platelet count, serum electrolytes (sodium, potassium, bicarbonate), renal function panel (blood urea nitrogen, creatinine and albumin level), liver function panel (aspartate and alanine transaminases and total bilirubin), markers of coagulation [international normalized ratio (INR) and D-dimer], markers of inflammation (CRP, ESR, procalcitonin and ferritin) and cardiac biomarkers [serum lactate, B-type natriuretic peptide (BNP) and troponin I].

Statistical analysis: Continuous data were compared using the Wilcoxon rank sum test. Categorical data were compared using the Chi-square or Fisher exact tests. Multivariate logistic regression was conducted to identify variables that would predict the diagnosis of MIS-C. Receiver operating characteristic curves were obtained using sensitivity analysis for individual variables to determine optimal cut-off values in predicting MIS-C. Statistical analysis was performed using JMP Pro 14.0 (SAS Institute). A P value <0.05 was considered statistically significant.

RESULTS

A total of 68 patients (42.7% male) were included in the study. 28 (41.2%) patients were diagnosed with MIS-C while 40 (58.8%) patients had SC-COVID-19. **Table I** provides demographics, clinical characteristics and outcomes of our cohort. Most patients were White (42.7%), and the median age was 10.6 (IQR 2.8-16.2) years and median weight was 42.3 (IQR 14.3-84.4 kg). MIS-C patients were more likely to be overweight/obese (P=0.02); 48 patients (70.6%) had at least one comorbidity. Comorbidities were significantly higher in SC-COVID-19 cohort (P=0.001). Indications for admission included respiratory failure, shock, seizures, pancreatitis, and diabetic ketoacidosis. Patients with respiratory failure requiring PAP or invasive ventilation, hemodynamic instability, diabetic ketoacidosis and Glasgow coma scale score <8 were admitted to PICU.

Higher prevalence of fever, rash and GI symptoms whereas a lower prevalence of cough and dyspnea were seen in MIS-C cohort (P<0.05). While higher proportion of patients with MIS-C required invasive mechanical ventilation (P<0.001) and inotropes (P=0.007), more patients with SC-COVID-19 required PICU admission (P=0.007). There was no difference in LOS and mortality among the two cohorts. MIS-C cohort had a significantly lower level of hemoglobin, platelet count, serum sodium, potassium, bicarbonate and albumin, and a significantly higher levels of total bilirubin, INR, D-dimer, CRP, procalcitonin, ESR and BNP (P<0.05). (**Table II**)

Upon multivariate logistic regression with outcome being MIS-C diagnosis, the best model was observed when CRP, platelet count, GI and mucocutaneus involvement and absence of respiratory involvement were incorporated in the model with performance of 0.94 (P<0.001) (**Web Table I**). On sensitivity analysis for individual variables, the optimal cut-offs to predict MIS-C were CRP ≥40 mg/L and platelet count <150 $\times 10^9$/L. Using these cut-offs, when both these criteria were fulfilled, the specificity to diagnose MIS-C was 97.5% whereas when neither of these criteria were fulfilled, the sensitivity was 96.4%. Similar specificity was observed when CRP ≥40 mg/L and mucocutaneous involvement were present. When both were absent, sensitivity to rule out MIS-C was 92.8%.

DISCUSSION

The results from this study suggest that elevated CRP, thrombocytopenia, GI and mucocutaneous involvement and absence of respiratory involvement at presentation can be helpful in differentiating MIS-C from SC-COVID-19 in children. A CRP value ≥40 mg/L with either platelet count <150 $\times 10^9$/L or mucocutaneous involvement had a high specificity of 97.5% to diagnose MIS-C.

A recent meta-analysis showed that presenting symptoms of SC-COVID-19 are non-specific and include fever, diarrhea, nausea, vomiting, malaise and fatigue [9].

Table I Demographics and Clinical Characteristics of Patients With MIS-C and Severe/Critical COVID-19

Parameters	*MIS-C (n=28)*	*Severe/critical COVID-19 (n=40)*	*P value*
Age (y)[a]	8.1 (3.1-12.9)	13.4 (2.7-16.9)	0.43
Male gender	10 (35.7)	19 (47.5)	0.33
Race			
White	13 (46.4)	16 (40)	0.82
Hispanic or Latino	7 (25)	9 (22.5)	
African American	4 (14.3)	9 (22.5)	
American Indian	2 (7.1)	3 (7.5)	
Asian	1 (3.6)	0 (0)	
Unknown	1 (3.6)	3 (7.5)	
Weight (kg)[a]	38 (14.9-63.9)	49.8 (13.2-96.9)	0.51
Underweight	0	10 (25)	0.02
Normal weight	15 (53.6)	26 (65)	
Overweight/obese	13 (46.4)	4 (10)	
Comorbidity			
Any	13 (46.4)	35 (87.5)	<0.001
>2	4 (14.3)	23 (57.5)	<0.001
>3	3 (10.7)	18 (45)	0.003
>4	2 (7.1)	11 (27.5)	0.04
Comorbidities			
Asthma	4 (14.3)	9 (22.5)	0.40
Genetic/metabolic condition	2 (7.1)	5 (12.5)	0.47
Epilepsy	0 (0)	7 (17.5)	0.02
Cerebral palsy	0 (0)	6 (15)	0.03
Congenital heart disease	0 (0)	5 (12.5)	0.05
Symptoms at presentation			
Fever	28 (100)	25 (62.5)	<0.001
Cough	4 (14.3)	15 (37.5)	0.03
Dyspnea	5 (17.9)	22 (55)	0.002
Vomiting	18 (64.3)	9 (22.5)	<0.001
Diarrhea	13 (46.4)	3 (7.5)	<0.001
Abdominal pain	14 (50)	3 (7.5)	<0.001
Reduced oral intake	14 (50)	10 (25)	0.03
Lethargy	8 (28.6)	14 (35)	0.58
Rash	17 (60.7)	2 (5)	<0.001
Systems involved			
Respiratory	12 (26.7)	33 (73.3)	<0.001
Gastrointestinal	21 (75)	15 (37.5)	0.002
Mucocutaneous	16 (57.1)	3 (7.5)	<0.001
Neurologic	4 (14.3)	4 (10)	0.59
Cardiac	13 (46.4)	7 (17.5)	0.01
Coinfections	8 (28.6)	14 (35)	0.58
PICU admission	9 (32.1)	26 (65)	0.007
Oxygen support	11 (39.3)	39 (97.5)	<0.001
Maximum oxygen support			
Invasive ventilation	5 (17.9)	1 (2.5)	0.0006
PAP	0	18 (45)	
Nasal cannula	6 (21.4)	20 (50)	
None	17 (60.7)	1 (2.5)	
Length of stay (d)[a]	5 (3-7)	2 (2-8)	0.72
Inotrope use	8 (28.6)	2 (5)	0.007
Mortality	0	1 (2.5)	0.30

Values in no. (%) or [a]median (IQR).

Table II Laboratory Markers at Presentation in Patients With MIS-C and Severe/ Critical COVID-19

Parameters	*MIS-C (N=28)*	*Severe/critical COVID-19 (N=40)*	*P value*
Blood counts, n=68			
Leukocyte count (x10^9/L)	9.7 (6.1-15.1)	7.5 (5.6-11)	0.16
Hemoglobin (g/dL)	11.1 (10.1-12.3)	13.1 (11.6-15)	<0.001
Platelet count (x10^9/L)	158 (96-248)	222 (199-334)	0.001
Metabolic panel, n=68			
Sodium (mEq/L)	136 (131-139)	139 (137-141)	<0.001
Potassium (mEq/L)	3.9 (3.5-4.1)	4.4 (3.9-4.9)	<0.001
Bicarbonate (mEq/L)	22.5 (20-25)	25 (23-27)	0.01
Albumin (g/dL)	3.9 (3.5-4.3)	4.4 (3.9- 4.8)	0.02
Blood urea nitrogen (mg/dL)	12 (9-17)	12 (8-15)	0.66
Creatinine (mg/dL)	0.6 (0.4-0.8)	0.5 (0.4-0.9)	0.70
Aspartate aminotransferase (units/L)	51 (26-85)	48 (35-75)	0.98
Alcanine aminotransfercase (units/L)	48 (26-89)	31 (18-71)	0.07
Total bilirubin (mg/dL)	0.6 (0.4-1.1)	0.4 (0.2-0.7)	0.002
Coagulation markers			
International normalized ratio, *n*=50	1.3 (1.25-1.45)	1.2 (1.1-1.25)	<0.001
D-dimer (ng/mL), *n*=52	1130 (801-1971)	294 (222-1750)	0.003
Inflammatory markers			
Procalcitonin (ng/mL), *n*=50	2.3 (0.7-12.5)	0.1 (0.05-0.33)	<0.001
C-reactive protein (mg/L), *n*=68	142 (76-189)	14 (2.3-55)	<0.001
Erythrocyte sedimentation rate (mm/h), *n*=44	35 (24-76)	15 (6-62)	0.02
Ferritin (ng/mL), *n*=43	522 (163-1618)	256 (116-772)	0.20
Cardiac markers			
Lactate (mmol/L), *n*=35	1.6 (1.2-2.9)	1.5 (1-2.4)	0.70
Brain natriuretic peptide (pg/mL), *n*=58	101 (30-251)	25 (9-81)	0.007
Troponin (ng/mL), *n*=57	0.01 (0.01-0.04)	0.01 (0.01-0.02)	0.15

Value in median (IQR) MIS-C - multisystem inflammantory syndrome in children; COVID-19 - coronavirus disease 2019.

Similarly, MIS-C is also characterized by non-specific symptoms [10]. Moreover, both conditions can present with septic shock and multiorgan dysfunction [6,10].

The association of thrombocytopenia with MIS-C observed in this study is of particular importance. Thrombocytopenia has been associated with severity and poor outcomes in adults with active COVID-19 infection including ICU admission, progression to acute respiratory distress syndrome and death; however, such an association is not yet evident in children [11,12].

Cytokines like tumor necrosis factor-alpha and interleukin-10 have shown to distinguish between MIS-C and SC-COVID-19 [13]. However, cytokine profiling is time consuming and expensive. Our study used routinely obtained laboratory markers in combination to predict MIS-C. We believe that using such refined parameters will help in differentiating MIS-C from SC-COVID-19 infection in real time.

We also observed that a higher proportion of MIS-C patients were previously healthy. This is similar to previous reports [13]. A plausible explanation for this observation is a higher cytokine storm in previously healthy children leading to a severe immune response. Children with comorbidities are probably more likely to get severe infections and require more respiratory support as seen in SC-COVID-19 cohort [14]. Although, a higher proportion of MIS-C patients required inotropes and invasive ventilation, they were less likely to be admitted to PICU, as also previously reported [5]. This could be explained by higher proportion of SC-COVID-19 patients requiring oxygen therapy, especially PAP.

Our study has some limitations. Due to its retrospective nature, there is a possibility of potential unknown confounders being missed. As the sample size was limited, findings can only be considered as suggestive. Reference ranges for laboratory values are different at various institutions and the cut-off of CRP ≥40 mg/L might not be applicable.

In conclusion, elevated CRP in combination with either thrombocytopenia or mucocutaneous involvement is

WHAT THIS STUDY ADDS?

- Elevated CRP (≥40 mg/L) with either thrombocytopenia (platelet count <150x10^9/L) or mucocutaneous involvement is helpful in differentiating MIS-C from severe/critical SARS-CoV-2 infection.

supportive of MIS-C diagnosis. Thus, these routinely obtained markers may be useful in differentiating these two conditions and thus, aide in appropriate management of these patients. Since treatment options for these conditions differ, the findings from this study could be used for timely identification of patients with MIS-C, counsel families and plan appropriate treatment accordingly.

Ethics clearance: University of Oklahoma Institutional Review Board; No. 12928 dated December 31, 2020.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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