Performance of Cytokine Storm Syndrome Scoring Systems in Pediatric COVID-19 and Multisystem Inflammatory Syndrome in Children

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Objective. The objective of this study is to evaluate pediatric patients using existing macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) scoring systems to determine how these systems identify patients with cytokine storm syndrome (CSS) in the setting of a multisystem inflammatory syndrome in children (MIS-C) and active coronavirus disease 2019 (COVID-19) infection.

Methods. Hospitalized pediatric patients with MIS-C and active COVID-19 infection at a single institution were identified. Infectious data, clinical findings, and laboratory values were collected, and patients were stratified by disease severity. Eight historically used scoring systems for MAS, HLH, and CSS were examined in the cohort of patients with MIS-C and pediatric COVID-19.

Results. The HLH-2004 criteria and HScore did not identify any patients as having CSS on admission, with only one patient with COVID-19 meeting criteria at peak disease severity. The 2016 systemic juvenile idiopathic arthritis (sJIA)/MAS criteria, ferritin/erythrocyte sedimentation rate (ESR) ratio, and COVID-19 CSS Quick Score most frequently identified CSS in this population and distinguished between COVID-19 and MIS-C hyperinflammation. The 2019 MAS/sJIA (MS) score and the COVID-19–associated hyperinflammatory syndrome (cHIS) criteria were less likely to identify CSS, as the MS score overestimated CSS and the cHIS resulted in similar scores regardless of severity or disease type. The Caricchio COVID-Cytokine Storm (COVID-CS) criteria identified patients with COVID-19 frequently but was less useful in MIS-C because of its COVID-19-specific criteria.

Conclusion. MIS-C and pediatric COVID-19 result in relatively unique CSSs and patterns of inflammation. Existing scoring systems for CSSs likely do not capture the full breadth of this disease process in MIS-C and pediatric COVID-19.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), remains a global pandemic numbering more than 100 million cases and 2 million deaths worldwide. In severe cases of COVID-19, there is significant evidence for overlap with cytokine storm syndromes (CSSs), complicating this disease process (1). CSS is a term first used in the literature to describe an inflammatory syndrome after stem cell transplantation (2,3). However, more recently, it has been used to define a broad family of syndromes, including familial or primary hemophagocytic lymphohistiocytosis (HLH), secondary or reactive HLH due to underlying infectious processes, macrophage activation syndrome (MAS) due to systemic juvenile idiopathic arthritis (sJIA) or other rheumatic diseases, and cytokine release syndrome in the setting of cancer treatments and chimeric antigen receptor T cell therapies (3,4).

Regardless of nomenclature, this family of CSS has as its cause uncontrolled immune activation and hyperinflammation typified by excessive cytokine release (1). There is a proportion of pediatric COVID-19 cases with CSS features leading to respiratory and end organ failure, but overall COVID-19 has been much a clinical trial for macrophage activation syndrome adjudication committee chair. No other disclosures relevant to this article were reported.

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less deadly in the pediatric population, with cases more likely to be mild or asymptomatic (5). However, multisystem inflammatory syndrome in children (MIS-C) has emerged as a rare postinfectious pediatric condition arising 3 to 4 weeks after the initial COVID-19 infection and characterized by similar hyperinflammation, severe shock, and organ dysfunction seen in other forms of CSS (6).

Before the SARS-CoV-2 pandemic, scoring systems have been used to identify different syndromes within the CSS family, including the HLH-2004 criteria and HScore (7,8), but more recent, specific scoring systems have been developed to help providers more rapidly identify patients with emerging CSS related to COVID-19. These scoring systems, including the COVID-19–associated hyperinflammatory syndrome (chIS) score, the Caricchio COVID-Cytokine Storm (COVID-CS) score, and the CSS Quick Score, have all been used in identifying adults with CSS related to COVID-19 (9–11). CSS scores exist in the pediatric population as well, but all are specific to patients with sJIA complicated by MAS: the ferritin/erythrocyte sedimentation rate (ESR) ratio, the 2019 MAS/sJIA (MS) score, and 2016 sJIA/MAS score (12–14). In this study, we use the aforementioned CSS scoring systems to determine how they identify CSS among a cohort of patients with MIS-C and severe COVID-19 at our institution.

PATIENTS AND METHODS

A retrospective review of all patients less than 22 years of age hospitalized with active COVID-19 infection and MIS-C were identified from April 1 to December 31, 2020, at Children’s of Alabama hospital in Birmingham, AL. Patients were identified from the electronic medical record using International Classification of Diseases, 10th Revision (ICD-10) codes for active COVID-19 pneumonia (ICD-10 U07.1) and MIS-C (ICD-10 U07.1, M35.81) and further verified using positive infectious, serologic, and clinical data. Clinical notes were reviewed for documentation of COVID-19 infection, MIS-C criteria, patient demographics, hospital course, and laboratory data. Patients with MIS-C were divided into mild and severe types: mild MIS-C was defined as patients meeting US Centers for Disease Control and Prevention (CDC) case definition of MIS-C without requiring vasopressor or positive pressure ventilation, whereas patients with severe MIS-C met CDC criteria and required vasopressor administration and/or positive pressure ventilation. Patients with severe COVID-19 were selected out of the hospitalized population and defined as having positive COVID-19 polymerase chain reaction (PCR) testing results with a primary diagnosis of COVID-19 pneumonia, requiring positive pressure ventilation or vasopressor administration, and/or having end organ failure.

Using laboratory data, presenting signs/symptoms, and hospital course, scores were calculated per the aforementioned CSS scoring systems. Scoring criteria and calculations are summarized in Supplementary Table 1. Continuous variables are reported as medians and interquartile ranges, and categorical variables are summarized as frequencies and percentages. Comparisons of nonparametric laboratory values were made using the Kruskal-Wallis test at a P value of 0.05. This study was approved by the University of Alabama at Birmingham Institutional Review Board via decision number IRB-140306007.

RESULTS

Demographics and clinical characteristics. Twelve patients who met the previously discussed definition for severe COVID-19 were identified. Forty-one patients with MIS-C were identified, 23 classified as mild and 18 as severe (Table 1). The median age in patients with COVID-19 was 15.5 years (interquartile range [IQR], 2.75-18) and was 11 years (IQR, 7-13) in patients with MIS-C. The majority of both groups was male. The majority of patients with MIS-C was Black or African American (54%), followed by White/non-Hispanic (32%) and Hispanic (15%). The racial disparity was more muted in patients with COVID-19, with non-Hispanic White and Black/African American patients equaling 42% of patients, followed by Hispanic at 17%. A majority of patients with MIS-C were found to be previously healthy at baseline, with 90% of patients without any underlying medical problems; existing medical conditions included asthma and obesity. Conversely, 83% of patients with COVID-19 had at least one chronic medical condition, including neurodevelopmental disorders, congenital heart disease, diabetes, and chronic lung disease. A majority of patients with MIS-C reported fever (95%), gastrointestinal symptoms (93%) (nausea, vomiting, abdominal pain, and diarrhea), rash (54%), and conjunctivitis (63%) as the most common presenting symptoms on admission. Alternatively, a majority of patients with COVID-19 presented with fever (67%) and respiratory symptoms (92%) (hypoxia, shortness of breath, and cough), a minority reported gastrointestinal symptoms (25%), and no patients noted rash, conjunctivitis, or mucosal changes. All patients with severe COVID-19 were admitted to the intensive care unit (ICU) to receive vasopressors (58%) and/or positive pressure ventilation (92%). Fifty-four percent of patients with MIS-C required ICU admission for vasopressors (44%) and/or positive pressure ventilation (15%). By definition, all patients with COVID-19 were SARS-CoV-2-positive on PCR; only two patients were tested for antibodies, neither positive. Almost all patients...
with MIS-C tested positive for SARS-CoV-2 antibodies (97%, 37 of 38), and 34% were positive on SARS-CoV-2 PCR testing as well. Two patients with MIS-C (bacterial pneumonia and ruptured appendix) and one patient with COVID-19 (urinary tract infection) in this population were treated for an additional infectious agent during the study period.

**Laboratory values.** Both patients with MIS-C and patients with COVID-19 had relatively normal white blood cell (WBC) counts, with neutrophilic predominance on admission and lymphopenia, which worsened throughout hospitalization (Table 2). Statistical significance was found between patients with severe MIS-C and patients with severe COVID-19 regarding hemoglobin.

| Table 1. Demographics and clinical characteristics |
|---------------------------------------------------|
| **Demographics** | Mild MIS-C (n = 23) | Severe MIS-C (n = 18) | MIS-C (n = 41) | Severe COVID-19 (n = 12) |
| Age, y Median (IQR) | 10 (6.5-13.5) | 11.5 (10-13) | 11 (7-13) | 15.5 (2.75-18) |
| Sex, No. (%) | | | | |
| Male | 11 (48) | 14 (78) | 25 (61) | 8 (67) |
| Race, No. (%) | | | | |
| White | 9 (39) | 4 (22) | 13 (32) | 5 (42) |
| Black | 10 (42) | 12 (67) | 22 (54) | 5 (42) |
| Other | 4 (17) | 2 (11) | 6 (15) | 2 (17) |
| Ethnicity, No. (%) | | | | |
| Hispanic | 4 (17) | 2 (11) | 6 (15) | 2 (17) |
| Non-Hispanic | 19 (83) | 16 (89) | 35 (85) | 10 (83) |
| Underlying conditions, No. (%) | | | | |
| Previously healthy | 21 (91) | 16 (89) | 37 (90) | 2 (17) |
| Any underlying medical condition | 2 (9) | 2 (11) | 4 (10) | 10 (83) |
| Obesity | 0 (0) | 1 (6) | 1 (2) | 2 (17) |
| Asthma | 0 (0) | 1 (6) | 3 (7) | 1 (8) |
| Chronic lung disease | 0 (0) | 0 (0) | 0 (0) | 2 (17) |
| Autoimmune Dx | 0 (0) | 0 (0) | 0 (0) | 1 (8) |
| Diabetes | 0 (0) | 0 (0) | 0 (0) | 2 (17) |
| Congenital heart disease | 0 (0) | 0 (0) | 0 (0) | 3 (25) |
| Neurodevelopmental Dx | 0 (0) | 0 (0) | 0 (0) | 6 (50) |
| Symptoms on presentation, No. (%) | | | | |
| Fever | 23 (100) | 16 (89) | 39 (95) | 8 (67) |
| Respiratory symptoms | 3 (13) | 0 (0) | 3 (7) | 11 (92) |
| Ptosis | 0 (0) | 0 (0) | 0 (0) | 8 (67) |
| Cough | 2 (9) | 0 (0) | 2 (5) | 5 (42) |
| Shortness of breath | 1 (4) | 0 (0) | 1 (2) | 6 (50) |
| Gastrointestinal symptoms | 21 (91) | 17 (94) | 38 (93) | 3 (25) |
| Nausea/vomiting | 15 (65) | 11 (61) | 26 (63) | 3 (25) |
| Diarrhea | 12 (52) | 12 (67) | 24 (59) | 1 (8) |
| Abdominal pain | 15 (65) | 12 (67) | 27 (66) | 0 (0) |
| Rash | 16 (70) | 6 (33) | 22 (54) | 0 (0) |
| Conjunctivitis | 16 (70) | 10 (56) | 26 (63) | 0 (0) |
| Mucosal changes | 4 (17) | 5 (28) | 9 (22) | 0 (0) |
| Level of admission, No. (%) | | | | |
| Intensive care | 4 (17) | 18 (100) | 22 (54) | 12 (100) |
| Acute care | 19 (83) | 0 (0) | 19 (46) | 0 (0) |
| SARS-CoV-2 positivity, No. (%) | | | | |
| PCR | 9 (39) | 5 (28) | 14 (34) | 12 (100) |
| IgG antibodies, No./total No. (%) | 21/22 (95) | 16/16 (100) | 37/38 (97) | 0/2 (0) |
| Additional infectious agent, No. (%) | | | | |
| Viral | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Bacterial | 2 (9) | 0 (0) | 2 (5) | 1 (8) |
| Vasopressor requirement, No. (%) | | | | |
| Yes | 0 (0) | 18 (100) | 18 (44) | 7 (58) |
| No | 23 (100) | 0 (0) | 23 (56) | 5 (42) |
| Maximum respiratory support, No. (%) | | | | |
| None | 17 (74) | 3 (17) | 20 (49) | 0 (0) |
| Low-flow oxygen | 4 (17) | 7 (39) | 11 (27) | 1 (8) |
| High-flow oxygen | 2 (9) | 2 (11) | 4 (10) | 0 (0) |
| Positive pressure ventilation | 0 (0) | 6 (33) | 6 (15) | 11 (92) |

Abbreviations: COVID-19, coronavirus disease 2019; Dx, diagnosis; IgG, immunoglobulin G; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
levels on admission. Patients with MIS-C had low to normal platelet counts on admission, with not much downtrend during hospitalization, whereas patients with COVID-19 patients had a similar low to normal platelet count on admission but had a more robust decrease during hospitalization. Inflammatory markers were elevated in all groups, but patients with severe MIS-C had statistically higher C-reactive protein (CRP) and ESR levels as compared with patients with severe COVID-19. Liver enzyme level elevation was

| Laboratory values                                      | Mild MIS-C (n = 23) | Severe MIS-C (n = 18) | MIS-C (n = 41) | Severe COVID-19 (n = 12) | Severe MIS-C vs. severe COVID-19 |
|--------------------------------------------------------|---------------------|-----------------------|---------------|--------------------------|---------------------------------|
| White blood cell count, 10^9/μl                         |                     |                       |               |                          |                                 |
| Admission                                              | 10.1 (7.1-14.4)     | 10.2 (8.7-12.8)       | 10.1 (7.9-12.8)| 11.4 (9.1-15.8)          | 0.472                           |
| Absolute lymphocyte count, 10^9/μl                      |                     |                       |               |                          |                                 |
| Admission                                              | 1.09 (0.76-1.71)    | 0.76 (0.5-1.5)        | 0.99 (0.66-1.65)| 1.08 (0.59-1.51)         | 0.465                           |
| Minimum                                                | 0.71 (0.57-1.31)    | 0.69 (0.5-0.98)       | 0.71 (0.51-1.11)| 0.59 (0.4-0.87)          | 0.611                           |
| Absolute neutrophil count, 10^9/μl                      |                     |                       |               |                          |                                 |
| Admission                                              | 7.6 (5.4-10.9)      | 9.2 (7.1-11.3)        | 8.1 (5.9-11.2)| 8.4 (6.2-13.5)           | 0.825                           |
| Hemoglobin, g/dl                                        |                     |                       |               |                          |                                 |
| Admission                                              | 11.6 (10.5-12.6)    | 10.8 (9.9-11.5)       | 11.0 (10.3-12.3)| 12.7 (10.8-15)           | 0.028*                          |
| Minimum                                                | 9.6 (8.6-10.8)      | 8.2 (7.3-8.7)         | 8.8 (8.9-8.8)| 8.2 (7.6-10.4)           | 0.363                           |
| Platelet count, 10^9/μl                                 |                     |                       |               |                          |                                 |
| Admission                                              | 205 (152.5-268)     | 170 (126.8-200.5)     | 180 (135-230) | 198 (149.3-251-8)        | 0.290                           |
| Minimum                                                | 173 (114.5-239.5)   | 164.5 (110.3-188.5)   | 173 (111-208) | 84 (46.3-204.5)          | 0.446                           |
| C-reactive protein, mg/dl                              |                     |                       |               |                          |                                 |
| Admission                                              | 16.4 (9.4-19.9)     | 22.5 (16-28.1)        | 17.7 (12.6-25.6)| 7.79 (1.4-11.9)          | 0.0004*                         |
| Maximum                                                | 20.05 (14-23.2)     | 26.83 (19-29.6)       | 20.6 (16.6-27.6)| 14.8 (10.5-20.7)         | 0.013*                          |
| Erythrocyte sedimentation rate, mm/h                   | 37 (28-51)          | 58 (39.5-71)          | 45 (32-59.3) | 16 (9.35-31)             | 0.001*                          |
| Ferritin, ng/ml                                         | 331.5 (179.9-560.1) | 6871 (388.8-15276)    | 4868 (2481-1789.1)| 739.2 (281-1998.3)       | 0.866                           |
| Maximum                                                | 416.4 (263.3-7971)  | 949 (608.1-15276)     | 681.5 (354.1-1326.3)| 912.1 (454.3-2370)       | 0.832                           |
| Albumin, g/dl                                          | 3.6 (3.4-3.95)      | 3.3 (2.58-3.53)       | 3.5 (3.15-3.8) | 3.6 (3.1-4.3)            | 0.082*                          |
| Minimum                                                | 2.6 (2.33-2.7)      | 2.35 (1.83-2.5)       | 2.5 (2.1-2.63) | 2.6 (2.35-2.78)          | 0.103                           |
| Alanine transaminase, U/l                              | 29.8 (16-52)        | 28.7 (19.7-58.4)      | 29 (16.2-52.9) | 37.4 (16.4-48.4)         | 0.877                           |
| Maximum                                                | 49.1 (24.9-55.6)    | 37.2 (27.6-59.7)      | 45.8 (27.5-57.9)| 54.3 (39-75.6)           | 0.227                           |
| Aspartate transaminase, U/l                            | 42 (23-52.5)        | 42 (25-47)            | 42 (23.8-52.3) | 54.5 (27.3-126.5)        | 0.413                           |
| Maximum                                                | 55.5 (30.3-82)      | 46 (30-59)            | 47 (30-65.8)  | 56 (25.5-159)            | 0.028*                          |
| Brain natriuretic peptide, pg/ml                       | 37.8 (10-97.1)      | 1101.8 (208.6-1844.8)| 88.2 (176-1012.2)| 39.9 (24.6-111.4)        | 0.047                           |
| Maximum                                                | 607.4 (186.1-1993.8)| 1811.5 (1001.3-29279)| 126.3 (50.4-1024.7)| 0.014*                   |                                 |
| Troponin, ng/ml                                         | 0.01 (0.01-0.04)    | 0.2 (0.03-0.81)       | 0.03 (0.01-0.26)| 0.02 (0.01-0.07)         | 0.150                           |
| Maximum                                                | 0.05 (0.01-0.24)    | 0.4 (0.09-1.65)       | 0.14 (0.03-0.61)| 0.06 (0.02-0.97)         | 0.238                           |
| Lactate dehydrogenase, U/l                             | 308 (244-486)       | 264 (213-310)         | 283 (225-353.5)| 818 (627-1115)           | 0.001*                          |
| Maximum                                                | 373.5 (305.8-501.5) | 268 (244.5-306)       | 309 (245-486) | 820 (660-1115)           | 0.0002*                         |
| D-dimer FEU, μg/ml                                     | 2.14 (1.4-3.6)      | 3.37 (2.72-4.38)      | 2.98 (1.58-3.83)| 1.93 (0.85-2.06)         | 0.021*                          |
| Maximum                                                | 3.3 (1.9-4.04)      | 6.03 (3.76-9.2)       | 3.76 (2.25-6.29)| 2.32 (1.94-2.66)         | 0.009*                          |
| Fibrinogen, mg/dl                                      | 504 (401.5-601)     | 576.5 (470.8-635-8)   | 535 (444-635) | 366.5 (282.8-459.5)      | 0.007*                          |
| Minimum                                                | 407 (255.5-477)     | 340 (251.3-465.5)     | 391 (252-470) | N/A                      | N/A                             |
| Maximum                                                | 591 (418-675.5)     | 589.5 (492-3.781.5)   | 591 (473-663) | N/A                      | N/A                             |

Abbreviations: COVID-19, coronavirus disease 2019; FEU, fibrinogen equivalent units; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; N/A, not available.

* denotes statistical significant for p<0.05.
somewhat similar in both groups, with slight elevation noted and with statistical significance only noted in Aspartate aminotransferase levels at peak disease activity. Brain natriuretic peptide levels were elevated in patients with MIS-C on admission and during hospitalization, with patients with severe COVID-19 having significantly lower levels as compared with patients with severe MIS-C. Troponin levels were fairly similar between both groups. Patients with severe COVID-19 were noted to have significantly higher levels of lactate dehydrogenase (LDH), and patients with severe MIS-C had significantly higher d-dimer and fibrinogen levels on admission and during hospitalization.

**CSS scoring systems.** On admission, none of the patients with MIS-C or COVID-19 met HLH-2004 criteria, with only one patient with MIS-C (2%) and no patients with COVID-19 meeting criteria at any point during hospitalization (Table 3). Similarly, none of the patients with MIS-C met the threshold for a positive HScore either on presentation (median, 19; IQR, 0-46) or during admission (median, 68; IQR 49-79). Likewise, no patients with COVID-19 met HScore criteria on admission (median, 50.5; IQR, 13.5-72.25), but 25% of those patients went on to meet the threshold score during hospitalization (median, 101; IQR, 55.75-142.5), and those three patients had scores ranging from 189 to 215. For the 2016 sJIA/MAS criteria, 7% of patients with MIS-C met criteria on admission, with all of the positive patients from the severe MIS-C category. This percentage increased to 24% of all patients with MIS-C, with 17% of mild cases and 33% of severe cases meeting criteria during hospitalization. More patients with COVID-19 were identified using the 2016 sJIA/MAS criteria, with 25% and 50% of patients meeting criteria on presentation and during hospitalization, respectively. Alternatively, a majority of both patients with MIS-C and patients with COVID-19 met the threshold for a positive 2019 MS score.

Fifty-four percent of all patients with MIS-C were identified on presentation, including 48% of mild cases and 61% of severe cases. During admission, this increased to 76% of MIS-C cases, with 70% of mild cases and 83% of severe cases identified. Eighty-three percent of patients with COVID-19 met the MS score threshold on admission, increasing to 100% during hospitalization. The ferritin/ESR ratio was met on admission at the different 11.3 and 21.5 thresholds by 37% and 17% of patients, respectively. Alternatively, a majority of both patients with MIS-C and patients with COVID-19 met the threshold for a positive 2019 MS score.

Table 3. Performance of cytokine scoring systems in MIS-C and pediatric COVID-19

| On admission | Mild MIS-C | Severe MIS-C | Total MIS-C | Severe COVID-19 |
|--------------|------------|--------------|-------------|----------------|
| HLH-2004     | 0/23 (0%)  | 0/18 (0%)    | 0/41 (0%)   | 0/12 (0%)     |
| HScore >169  | 0/23 (0%)  | 0/18 (0%)    | 0/41 (0%)   | 0/12 (0%)     |
| HScore, median (IQR) | 19 (0 to 46) | 19 (19 to 51.25) | 19 (0 to 49) | 50.5 (13.5 to 72.25) |
| 2016 sJIA/MAS criteria | 0/23 (0%) | 3/18 (16.7%) | 3/41 (7%) | 3/12 (25%) |
| 2019 MS score >=2.1 | 1/23 (4%) | 11/41 (27%) | 11/52 (21%) | 10/12 (83%) |
| Ferritin/ESR ratio >11.3 | 8/23 (35%) | 7/18 (38.9%) | 15/41 (37%) | 10/12 (83%) |
| Ferritin/ESR ratio >21.5 | 2/23 (9%) | 5/18 (27.8%) | 7/41 (17%) | 9/11 (82%) |
| Ferritin/ESR ratio, median (IQR) | 7.56 (6.16 to 13.94) | 11.22 (7.64 to 25.35) | 9.65 (6.23 to 15.51) | 45.47 (32.36 to 86.9) |
| Caricchio COVID-CS criteria | - | - | - | 2/11 (18%) |
| chIS criteria, median (IQR) | 3 (2 to 4) | 4 (3 to 4.75) | 3 (3 to 4) | 2.5 (1 to 3.25) |
| COVID-19 CSS Quick Score | 9/23 (39%) | 9/17 (52.9%) | 18/40 (45%) | 1/12 (8%) |
| During hospitalization |  |  |  |  |
| HLH-2004     | 0/23 (0%)  | 1/18 (5.6%)  | 1/41 (2%)   | 0/12 (0%)     |
| HScore >169  | 0/23 (0%)  | 0/18 (0%)    | 0/41 (0%)   | 0/12 (0%)     |
| HScore, median (IQR) | 68 (49 to 68) | 68 (52 to 100.25) | 68 (49 to 79) | 101 (55.75 to 142.5) |
| 2016 sJIA/MAS criteria | 4/23 (17%) | 6/18 (33.3%) | 10/41 (24%) | 6/12 (50%) |
| 2019 MS score >=2.1 | 16/23 (70%) | 15/18 (83.3%) | 31/41 (76%) | 12/12 (100%) |
| 2019 MS score, median (IQR) | -1.4 (-2.08 to -0.78) | -0.56 (-1.84 to 0.69) | -0.91 (-1.97 to 0.47) | 1.69 (0.59 to 2.43) |
| Ferritin/ESR ratio >11.3 | 12/23 (52%) | 11/18 (61.1%) | 23/41 (56%) | 10/11 (91%) |
| Ferritin/ESR ratio >21.5 | 5/23 (22%) | 7/18 (38.9%) | 12/41 (29%) | 9/11 (82%) |
| Ferritin/ESR ratio, median (IQR) | 12.04 (7.42 to 17.78) | 16.69 (12.48 to 34.48) | 13.95 (7.32 to 30.44) | 66.07 (33.57 to 102.89) |
| Caricchio COVID-CS criteria | - | - | - | 8/11 (73%) |
| chIS criteria, median (IQR) | 4 (2.5 to 4.5) | 4.5 (4 to 5) | 4 (3 to 5) | 4.5 (3 to 5) |
| COVID-19 CSS Quick Score | 15/23 (65%) | 12/17 (70.6%) | 27/40 (68%) | 10/12 (83%) |

Note: %” denotes those meeting CSS criteria. Abbreviations: cHIS, COVID-19–associated hyperinflammatory syndrome; COVID-19 CSS, COVID-19 Cytokine Storm; COVID-19, coronavirus disease 2019; CSS, cytokine storm syndrome; ESR, erythrocyte sedimentation rate; HLH, hemophagocytic lymphohistiocytosis; IQR, interquartile range; MAS, macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; MS, MAS/sJIA; sJIA, systemic juvenile idiopathic arthritis.
91% and 82% of cases, respectively. The Caricchio COVID-CS criteria were unable to be calculated in patients with MIS-C, as the majority of requirements was specific to active COVID-19 pneumonia. Only 18% of the COVID-19 group met criteria on admission, but this increased to 73% during the hospital stay. The cHIS criteria noted a median value of 3 (IQR, 3-4) for patients with MIS-C on presentation, increasing to 4 (IQR, 3-5) during hospitalization. Patients with COVID-19 had a median cHIS score of 2.5 (IQR, 1-3.25) on presentation, increasing to 4.5 (IQR, 3-5) throughout their stay.

Finally, the COVID-19 CSS Quick Score identified 45% of patients with MIS-C on admission, somewhat higher than the 8% of patients with COVID-19 identified. However, this difference flipped during the hospital stay, as 68% of patients with MIS-C were identified as compared with 83% of patients with COVID-19.

**DISCUSSION**

In our analysis of the various CSS scoring systems and criteria available, there was a large variation in the proportion of patients identified. The HLH-2004 score did not identify CSS in any patients with MIS-C or COVID-19 on admission and only one patient with MIS-C at their peak disease activity during hospitalization, and the HScore similarly identified zero patients with MIS-C or COVID-19 initially and only three patients with COVID-19 during admission. On the other hand, the 2019 MS score and the COVID-19 CSS Quick Score identified CSS in the majority of patients with both disease processes, especially during hospitalization. When interpreting these findings, it becomes clear that subtle differences in the laboratory values and clinical findings used in each CSS scoring system result in their differential utility in identifying the pattern of inflammation seen in patients with MIS-C and patients with COVID-19. The emphasis on specific cytokine testing, bone marrow hemophagocytosis, and natural killer cell activity makes the HLH-2004 score less useful, as these have not been routinely tested in pediatric patients with MIS-C or COVID-19, and organomegaly has not been reported as a common finding (6). Additionally, the level of hyperferritinemia identified in our populations and in other MIS-C studies has been at a much lower degree than what would be required to meet criteria for the HScore, which, along with lack of organomegaly, makes it difficult to meet the HScore criteria (15). Alternatively, the 2019 MS score likely overestimated CSS in our population, as CNS involvement is one of the largest components of the score and is defined as anything from a headache to seizure, so a vast majority of patients met these criteria (16). This likely overestimation is seen in the fact that a large proportion of even mild MIS-C cases were identified as at risk for CSS by the MS score, showing that it does not do well at distinguishing disease severity.

In our cohort, the scores that seemed to be of some use were the 2016 sJIA/MAS criteria, ferritin/ESR ratio, and COVID-19 CSS Quick Score. The 2016 sJIA/MAS criteria distinguished between both mild and severe MIS-C and distinguished MIS-C from COVID-19. A ferritin/ESR ratio greater than 21.5 and the COVID-19 CSS Quick Score were able to distinguish MIS-C from COVID-19 but did not do well at stratifying MIS-C disease severity. When delving into their specifics to determine what differentiated these criteria from the alternatives, the laboratory studies involved are those that have been shown to be different in COVID-19 and MIS-C and are those that are routinely tested in most cases of these disease processes. Prior studies have shown specific differences in inflammation patterns of patients with pediatric COVID-19 and patients with MIS-C, including higher levels of CRP, ESR, and d-dimer in patients with MIS-C, higher levels of lactate dehydrogenase and lower platelet counts in patients with COVID-19, and differences in WBC patterns with higher neutrophil/lymphocyte ratios in patients with MIS-C (17,18). Our results of statistical significance in CRP, ESR, LDH, and d-dimer levels support these findings. The 2016 sJIA/MAS criteria, ferritin/ESR ratio, and COVID-19 CSS Quick Score key in on these differences, allowing for stratification between patients with mild and severe MIS-C, as well as between patients with MIS-C and COVID-19. Overall, both MIS-C and pediatric COVID-19 seem to result in relatively unique CSSs with different patterns of inflammation from what is thought of as typical HLH and MAS, with some scores and criteria working better than others at identifying at-risk patients.

There were some notable limitations of this study. Our population likely underestimated the use of some scoring systems, as some laboratory studies that were routinely part of some criteria were not routinely measured, such as triglyceride levels and specific cytokines. Likewise, the 2016 sJIA/MAS, MS score, and ferritin/ESR ratio were initially formulated to be used in the specific sJIA population, so the use of these systems in the COVID-19 and MIS-C populations is a nonvalidated use and it is questionable as to the generalizability of the findings. Additionally, we identified unique patient groups based on the CDC classification of MIS-C and COVID-19 pneumonia; in reality, these two disease processes likely overlap, as approximately 30% of patients with MIS-C still test positive for SARS-CoV-2 via nasal PCR. However, our populations take into account cycle thresholds of PCR testing, with active infections having lower cycle thresholds as compared with MIS-C (19). Finally, there remains no true gold standard definition of CSS in the setting of SARS-CoV-2.

Pediatric COVID-19 infection and MIS-C are severe diseases causing significant morbidity in the pediatric population, and it is likely that a portion of this severity is caused by the CSS that accompanies these disease processes. The existing scoring systems and criteria that have been historically used to stratify risk for HLH, MAS, and CSS have varying use in identifying and stratifying these patients within the MIS-C and pediatric COVID-19 populations. This is likely due to the relatively unique patterns of inflammation seen in these diseases. However, a few of these scoring systems can likely be useful in predicting CSS and possibly even in distinguishing between MIS-C and COVID-19. Further study is needed into the pathogenesis of CSS in MIS-C and pediatric
COVID-19 to create more consistent and useful scoring systems to predict and prevent morbidity and mortality.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Reiff had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Cron and Reiff.

**Acquisition of data.** Reiff.

**Analysis and interpretation of data.** Reiff.

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