Distinguishing Multisystem Inflammatory Syndrome in Children From COVID-19, Kawasaki Disease and Toxic Shock Syndrome

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Background: Distinguishing multisystem inflammatory syndrome in children (MIS-C) from coronavirus disease 2019 (COVID-19), Kawasaki disease (KD), and toxic shock syndrome (TSS) can be challenging. Because clinical management of these conditions can vary, timely and accurate diagnosis is essential.

Methods: Data were collected from patients <21 years of age hospitalized with MIS-C, COVID-19, KD, and TSS in 4 major health care institutions. Patient demographics and clinical and laboratory data were compared among the 4 conditions, and a diagnostic scoring tool was developed to assist in clinical diagnosis.

Results: A total of 233 patients with MIS-C, 102 with COVID-19, 101 with KD, and 76 with TSS were included in the analysis. Patients with MIS-C had the highest prevalence of decreased cardiac function (38.6%), myocarditis (34.3%), pericardial effusion (38.2%), mitral regurgitation (31.8%) and pleural effusion (34.8%) compared with patients with the other conditions. Patients with MIS-C had increased peak levels of C-reactive protein and decreased platelets and lymphocyte nadir counts compared with patients with COVID-19 and KD and elevated levels of troponin, brain natriuretic peptide and pro-brain natriuretic peptide compared with COVID-19. Diagnostic scores utilizing clinical findings effectively distinguished MIS-C from COVID-19, KD, and TSS, with internal validation showing area under the curve ranging from 0.87 to 0.97.

Conclusions: Compared with COVID-19, KD, and TSS, patients with MIS-C had significantly higher prevalence of cardiac complications, elevated markers of inflammation and cardiac damage, thrombocytopenia, and lymphopenia. Diagnostic scores can be a useful tool for distinguishing MIS-C from COVID-19, KD, and TSS.

Key Words: COVID-19, MIS-C, Kawasaki disease, TSS

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Multisystem inflammatory syndrome in children (MIS-C) occurring after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first described in April 2020 in the United Kingdom and was quickly followed by descriptions of similar patients in other European countries and the United States.[1–3] In the United Kingdom, this condition was termed pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2.[4] Many patients with MIS-C had evidence of SARS-CoV-2 infection 2–6 weeks before illness onset.[1,3,5] In the United States, as of August 27, 2021, 4661 MIS-C patients had been reported to the Centers for Disease Control and Prevention (CDC).[6] Many patients diagnosed with MIS-C were reported to have asymptomatic infection or mildly symptomatic coronavirus disease 2019 (COVID-19) before their diagnosis of MIS-C. Most cases of COVID-19 in children reported in the literature are mild or asymptomatic, but severe disease and death have occurred.[7,8] Risk factors for severe COVID-19 include chronic conditions like asthma, diabetes, immunosuppression and obesity.[8,9]

Distinguishing MIS-C from COVID-19 and other hyperinflammatory conditions can be challenging for health care providers.

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The clinical features of MIS-C can substantially overlap with those of COVID-19, Kawasaki disease (KD), and toxic shock syndrome (TSS).[2,8,10–14] While the presence of anti–SARS-CoV-2 IgM or IgG has been a useful marker to distinguish MIS-C early in the pandemic, the specificity of seropositivity as a diagnostic test for MIS-C decreases as population immunity grows from ongoing exposure, COVID-19 illness, or following vaccination. Prompt recognition and identification of patients with MIS-C is important for appropriate and timely treatment.[15]

CDC initiated a multicenter collaborative project with the objective of collecting and analyzing demographic, clinical and laboratory data to better define the characteristics that distinguish MIS-C from COVID-19, KD and TSS. In addition, diagnostic scoring profiles were developed to provide simplified tools to help clinicians better distinguish MIS-C from COVID-19, KD and TSS.

METHODS

The study was conducted in collaboration with 4 institutions and approved by their retrospective Institutional Review Boards: Children's Healthcare of Atlanta and Emory University, Atlanta, Georgia; Phoenix Children's Hospital, Phoenix, Arizona; Arnold Palmer Hospital for Children/Orlando Health, Orlando, Florida and Washington University, St. Louis, Missouri. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[16] For MIS-C and COVID-19, medical records were reviewed for patients hospitalized from March 16, 2020, through February 21, 2021. For KD and TSS, inpatient medical records were reviewed during the pre–COVID-19 pandemic period of January 2019 through December 2019 to collect 100 cases of KD and October 2015 through December 2019 to collect 75 cases of TSS. To identify sufficient numbers of KD and TSS cases, patients diagnosed during the pandemic (starting from January 2020) were accepted if they tested negative for SARS-CoV-2.

Patients with MIS-C were <21 years of age, hospitalized with fever, multisystem involvement, laboratory evidence of inflammation, and positive SARS-CoV-2 test by reverse transcription polymerase chain reaction, serology, or antigen test. Patients with COVID-19 were <21 years of age, hospitalized with positive SARS-CoV-2 testing and with respiratory illness or at least two of the following symptoms (fever, chills, rigors, myalgia, headache, sore throat and new olfactory or taste disorder). Full descriptions of the MIS-C and COVID-19 case definitions, as well as the case definitions for KD and TSS, are provided in the Table, Supplemental Digital Content 1, http://links.lww.com/INF/E630. For MIS-C and COVID-19, the diagnoses were reviewed by a multidisciplinary team of clinicians at the hospitals. For a small number of patients in whom distinguishing between MIS-C and COVID-19 was challenging, CDC team members assisted in adjudicating the diagnosis that most clearly matched the patient's clinical manifestation. Patients with KD and TSS were deliberately obtained from the pre-pandemic period to avoid diagnostic confusion. For a subanalysis, patients with KD shock syndrome (KDSS) were compared with MIS-C and COVID-19 patients with shock (definition in the Table, Supplemental Digital Content 1, http://links.lww.com/INF/E630).[17]

Medical record abstraction for all 4 diseases was completed using the same case report form that was developed for MIS-C national surveillance with slight revisions to reflect the case definitions used for each disease (Form, Supplemental Digital Content 2, http://links.lww.com/INF/E631).[18] Information collected included patient demographics, clinical and laboratory characteristics, and illness outcomes. The peak and/or nadir laboratory values were collected but not the timing of laboratory results. Abstracted data were entered into a Research Electronic Data Capture database,[19,20] and statistical analyses were performed using R, version 4.0.2,[21] including the packages CatPredi,[22] mice,[23] glmnet,[24] WeightedROC,[25] and caret.[26] Patient demographics, clinical manifestations, outcomes and laboratory findings of patients with MIS-C were compared with those of COVID-19, KD and TSS. Mann-Whitney *U* tests were used to evaluate differences between diseases for continuous variables, and the Fisher exact test was used to assess differences for categorical variables.

Diagnostic scores were created to provide a simplified tool to help clinicians distinguish patients with clinical features that overlap with MIS-C and either one or multiple of the other three clinical conditions. The outcomes of these diagnostic scores are not intended to be a definitive diagnosis of MIS-C. The purpose of these scores is to use key clinical characteristics to quickly assess a patient's relative likelihood of having MIS-C in comparison to the other three conditions. Variables considered for these scores included comorbidities, clinical findings, and laboratory results. For easier clinical interpretation, continuous laboratory values were dichotomized using cutoff points that maximized discriminatory power between MIS-C and the other disease categories.[27] Multiple imputation by chained equations using fully conditional specification was used to account for patients missing dichotomized normal/abnormal values for select laboratory markers (Table, Supplemental Digital Content 3, http://links.lww.com/INF/E632).[23] Using least absolute shrinkage and selection operator (LASSO) for variable selection, models with a priori limit of 7 or fewer variables were identified for each diagnostic score.[24] Patient data in the least absolute shrinkage and selection operator models were weighted such that the number and age distribution of MIS-C patients effectively matched that of the non–MIS-C patients in each comparison. Patient totals were balanced so that the scores could be applied in a cohort with equal numbers of MIS-C and non–MIS-C patients. Generalized linear models were used to generate regression coefficients, which were converted to diagnostic score points via rounding with an adjustment factor to minimize error. The end product was a set of clinical criteria with assigned point totals. Weighted area under the curve (AUC) values were calculated to quantify model fit of the diagnostic scores.[25] In addition, the estimated probability of a patient having MIS-C based on the weighted regression results was calculated at each possible point total. To assess the generalizability of diagnostic scores, 10-fold internal cross-validation[28] was used to evaluate the performance of the scores in patient data sets not used for model estimation, and corresponding kappa statistics were computed for each diagnostic score.

RESULTS

Overall, 512 patients were identified from the 4 institutions: 233 (45.5%) with MIS-C, 102 (19.9%) with COVID-19, 101 (19.7%) with KD (92 with complete and 9 with incomplete KD), and 76 (14.8%) with TSS. MIS-C patients had illness onset from March 16, 2020, through March 8, 2021, and COVID-19 patients from March 24, 2020, through February 21, 2021. The majority of patients with KD (94%) and TSS (83%) were identified through retrospective chart review from the pre–COVID-19 pandemic period (October 2015 to December 2019).

Table 1 provides an overview of demographics and clinical outcomes of the patients. Among patients with MIS-C, 147 (63.1%) were male—a proportion similar to that of patients with KD (66; 65.3%) but greater than that of COVID-19 (40; 39.2%) and TSS (23; 30.3%; both $P < 0.001$). MIS-C patient ages [median, 9 years; interquartile range (IQR), 5–13] were generally lower than those of COVID-19 patients (median, 15 years; IQR, 3–17) and TSS patients (median, 13 years; IQR, 9–16) but greater than KD patients (median, 3 years; IQR, 2–5). Among patients with MIS-C, 44.1% were non-Hispanic Black, compared with 34.7% of patients with COVID-19 ($P = 0.139$) and 14.5% of patients with TSS

TABLE 1. Demographic and Clinical Overview of MIS-C, COVID-19, KD, and TSS Patients, United States

		COVID-19 (n = 102)		Kawasaki Disease (n = 101)		Toxic Shock Syndrome (n = 76)	
Variable	MIS-C (n = 233)	n (%)	*P* Value*	n (%)	*P* Value*	n (%)	*P* Value*
Sex							
Male	147 (63%)	40 (39%)	<0.001	66 (65%)	0.712	23 (30%)	<0.001
Age, y; median (IQR)	9 (5–13)	15 (3–17)	<0.001	3 (2–5)	<0.001	13 (9–16)	<0.001
Race/ethnicity†							
Hispanic	60 (27%)	32 (33%)	0.349	14 (14%)	0.014	5 (7%)	<0.001
Black, non-Hispanic	98 (44%)	34 (35%)	0.139	57 (58%)	0.030	10 (14%)	<0.001
White, non-Hispanic	52 (23%)	30 (31%)	0.211	14 (14%)	0.072	47 (68%)	<0.001
Asian, non-Hispanic	5 (2%)	1 (1%)	0.671	13 (13%)	<0.001	2 (3%)	0.671
AI/AN, non-Hispanic	2 (1%)	0 (0%)	1.000	0 (0%)	1.000	1 (1%)	0.557
Multiple	3 (1%)	1 (1%)	1.000	1 (1%)	1.000	0 (0%)	1.000
Other	2 (1%)	0 (0%)	1.000	0 (0%)	1.000	4 (6%)	0.030
Missing	11 (-)	4 (-)		2 (-)		7 (-)	
Days in hospital, median (IQR)‡	5 (4–8)	4 (2–8)	0.009	4 (3–5)	<0.001	4 (3–6)	0.080
1	1 (0%)	11 (12%)		0 (0%)		2 (3%)	
2–7	169 (74%)	58 (61%)		88 (87%)		57 (75%)	
8–14	50 (22%)	15 (16%)		9 (9%)		8 (11%)	
≥15	9 (4%)	11 (12%)		4 (4%)		9 (12%)	
ICU admission	145 (62%)	50 (49%)	0.030	11 (11%)	<0.001	62 (82%)	0.002
Days in ICU, median (IQR)§	3 (0–5)	7 (2–13)	0.001	5 (3–7)	0.073	1 (0–2)	0.174
Underlying medical conditions							
Obesity	84 (36%)	51 (50%)	0.021	13 (13%)	<0.001	19 (25%)	0.093
Chronic lung disease	24 (10%)	25 (25%)	0.001	5 (5%)	0.139	6 (8%)	0.658
Days with fever¶							
Total, median (IQR)	5 (4–7)	4 (2–6)	<0.001	7 (5–8)	<0.001	3 (2–5)	<0.001
At admission, median (IQR)	4 (3–5)	2 (0–4)	<0.001	4 (3–6)	0.002	1 (0–3)	<0.001
Outcome							
Died	0 (0%)	1 (1%)	0.304	0 (0%)	-	1 (1.3%)	0.246

*Compared with patients with MIS-C.
†Twenty-four with missing race/ethnicity.
‡Eleven patients had unknown length of hospital stay.
§One hundred forty-eight patients admitted to the ICU had unknown length of ICU stay.
¶Forty-four patients had unknown length of fever.
AI indicates American Indian; AN, Alaska Native; ICU, intensive care unit.

($P < 0.001$). Patients with MIS-C were less likely to be non-Hispanic Asian (2.3%) compared with those with KD (13.1%; $P < 0.001$). Patients with MIS-C generally had longer median hospital days (5 days) compared with patients with COVID-19 (4 days; $P = 0.009$) and patients with KD (4 days; $P < 0.001$). Over three-fifths (62.2%) of patients with MIS-C were admitted to an intensive care unit, which was higher than for COVID-19 (49.0%; $P = 0.030$) and KD (10.9%; $P < 0.001$) but lower than for patients with TSS (81.6%; $P = 0.002$). Two patients died, one with COVID-19 and one with TSS. There were no deaths among patients with MIS-C or KD.

As shown in Table 2, the clinical manifestations of MIS-C, COVID-19, KD, and TSS had substantial overlap. The clinical features of MIS-C included in the case definition [fever, inflammation, and multisystem (≥2 organs) involvement] were reported in 65% of COVID-19, 72% of KD, and 78% of TSS patients (Table 2). However, compared with patients with COVID-19, patients with MIS-C were more likely to have gastrointestinal symptoms such as abdominal pain (74.7% vs. 25.5%; $P < 0.001$), vomiting (62.7% vs. 40.2%; $P < 0.001$) and diarrhea (51.5% vs. 32.4%; $P = 0.001$), rash (50.2% vs. 11.8%; $P < 0.001$), conjunctival injection (61.5% vs. 3.0%; $P < 0.001$) and neck pain (22.3% vs. 1.0%; $P < 0.001$; Figure 1A). They were also more likely to have pleural effusion (34.8% vs. 2.0%; $P < 0.001$) and cardiovascular involvement, including shock (40.1% vs. 8.8%; $P < 0.001$), hypotension (57.9% vs. 14.7%; $P < 0.001$), decreased cardiac function (38.6% vs. 3.9%; $P < 0.001$), myocarditis (34.3% vs. 1.0%; $P < 0.001$), pericardial effusion (38.2% vs. 2.0%; $P < 0.001$), mitral regurgitation (31.8% vs. 2.9%; $P < 0.001$), and coronary artery abnormalities (15.0% vs. 2.9%; $P < 0.001$; Figure 1B). Compared with patients with MIS-C, patients with COVID-19 had a higher prevalence of respiratory manifestations, including cough (67.6% vs. 29.2%; $P < 0.001$), shortness of breath (59.8% vs. 34.3%; $P < 0.001$), and pneumonia (52.0% vs. 11.1%; $P < 0.001$).

Compared with MIS-C, patients with KD were more likely to have rash (96.0% vs. 50.2%; $P < 0.001$), conjunctival injection (94.1% vs. 61.8%; $P < 0.001$), and coronary artery abnormalities (28.7% vs. 15.0%; $P = 0.006$) but were significantly less likely to have all other cardiovascular outcomes, as well as gastrointestinal, neurologic, or renal involvement (Figure 1A and B). Patients with TSS had lower rates of shortness of breath (21.1% for TSS patients vs. 34.3% for MIS-C patients; $P = 0.032$), conjunctival injection (26.3% vs. 61.8%; $P < 0.001$), neck pain (9.2% vs. 22.3%; $P = 0.011$), and pleural effusion (11.8% vs. 34.8%; $P < 0.001$) but were more likely to have rash (88.2% vs. 50.2%; $P < 0.001$) and acute kidney injury (47.4% vs. 24.0%; $P < 0.001$).

A summary of laboratory findings is shown in Figure 2 and Table, Supplemental Digital Content 4, http://links.lww.com/INF/E633. Compared with patients with COVID-19 and KD, patients with MIS-C had higher peak C-reactive protein (CRP), fibrinogen, and ferritin and lower platelet and lymphocyte count nadir. D-dimer and cardiac biomarkers (troponin, brain natriuretic peptide, and pro-brain natriuretic peptide) were not frequently collected among patients diagnosed with KD and TSS; peak levels of these four laboratory tests were significantly higher in patients with MIS-C compared with patients with COVID-19.

Four diagnostic scores were developed to distinguish MIS-C from COVID-19, KD and TSS independently or as a group for

Table 2. Percentage of Patients With MIS-C, COVID-19, KD, and TSS Who Met Clinical Criteria for Each Disease*

Clinical Criteria Included in Case Definitions	Patient Diagnoses			
	MIS-C	COVID-19	KD	TSS
MIS-C clinical criteria	100%	65%	72%	78%
Fever	100%	78%	100%	93%
Inflammation	100%	77%	72%	82%
Multisystem (≥2 organs) involvement	100%	94%	100%	100%
Cardiac	97%	32%	42%	97%
Renal	25%	10%	3%	49%
Respiratory	76%	93%	51%	62%
Hematologic	99%	59%	27%	53%
Gastrointestinal	95%	77%	76%	92%
Dermatologic	73%	13%	100%	92%
Neurologic	51%	26%	6%	43%
COVID-19 clinical criteria	81%	100%	50%	71%
Pneumonia or ARDS	60%	68%	12%	49%
Cough or shortness of breath	49%	87%	44%	34%
At least two of other COVID-19 criteria†	13%	53%	2%	30%
KD clinical criteria	15%	3%	100%	1%
Fever ≥5 days or until IVIG	90%	31%	100%	36%
Rash	50%	12%	97%	88%
Conjunctival injection	62%	3%	96%	26%
Oral mucosal changes	18%	1%	99%	32%
Cervical lymphadenopathy	6%	0%	29%	4%
Peripheral extremity changes‡	-	-	87%	-
Coronary artery abnormalities	15%	3%	29%	3%

*Clinical criteria for toxic shock syndrome were not considered, as those data were generally not collected for patients with the other diseases.

†At least two of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat and new olfactory or taste disorder.

‡Includes edema, erythema or generalized or periungual desquamation; data were not collected for patients with MIS-C, COVID-19 or TSS.

ARDS indicates acute respiratory distress syndrome; IVIG, intravenous immunoglobulin.

patients with multiple overlapping clinical features (Figure 3). The first score in Figure 3A assesses the likelihood of a patient having MIS-C compared with COVID-19. Seven criteria were included in this diagnostic score, each corresponding to a specific number of points. Conjunctival injection, for example, had 3 points, and abdominal pain, hypotension/shock and pericardial effusion each had 2 points. The points corresponding to the patients' findings are then added to provide an overall summed score that correlates with the relative likelihood of MIS-C compared with COVID-19. Figure 3B–D outlines the diagnostic scores developed to distinguish MIS-C, respectively, from KD, TSS and patients with clinical manifestations overlapping with all 3 conditions. Assessment of the diagnostic scores using internal cross-validation indicated that the diagnostic scores in Figure 3A were effective at discriminating MIS-C from COVID-19 with a kappa value of 0.78 (AUC, 0.97). The diagnostic scores in Figure 3B and C also had good diagnostic accuracy with kappa values of 0.87 (AUC, 0.96) and 0.73 (AUC, 0.94), respectively. The score differentiating MIS-C from the 3 overlapping conditions had a kappa value of 0.57 (AUC, 0.87; Figure, Supplemental Digital Content 5, http://links.lww.com/INF/E634).

In a subanalysis, patients with MIS-C shock were compared with patients with COVID-19 shock and KDSS (Table, Supplemental Digital Content 6, http://links.lww.com/INF/E635). Compared with patients with KDSS, patients with MIS-C shock were more likely to report abdominal pain (77.0% vs. 27.3%; $P = 0.003$) and headache (49.2% vs. 0%; $P = 0.001$), whereas patients with KDSS were more likely to have coronary artery dilatation or aneurysm (63.6% vs. 17.7%; $P = 0.002$) and rash (90.9%–48.7%; $P = 0.009$). Patients with MIS-C shock had lower lymphocyte counts (median, 580/μL vs. 1350/μL) and shorter duration of fever (median, 5 vs. 7 days; $P = 0.020$). Differences between MIS-C shock and COVID-19 shock were generally similar to differences between all MIS-C patients and COVID-19 patients, including more frequent cardiac and gastrointestinal involvement in MIS-C shock patients and pneumonia in COVID-19 shock patients (Table, Supplemental Digital Content 6, http://links.lww.com/INF/E635).

DISCUSSION

MIS-C, COVID-19, KD and TSS are all conditions with the potential for multisystem involvement and systemic inflammation, yet they are distinct disorders with potentially different underlying pathophysiology that require different approaches for clinical management. The present study highlights demographic, clinical and laboratory differences among the 4 disorders that can assist in establishing a diagnosis and optimal management of affected children. MIS-C was more commonly associated with abdominal pain, diarrhea, decreased cardiac function, myocarditis, pericardial effusion, mitral regurgitation, pleural effusion and neck pain. Decreased cardiac function, myocarditis, pericardiac effusion, mitral regurgitation and pleural effusion occurred almost exclusively in patients with MIS-C.[29] Patients with COVID-19 had the highest rates of cough, shortness of breath and pneumonia with the lowest rates of cardiovascular complications and dermatologic symptoms. Patients

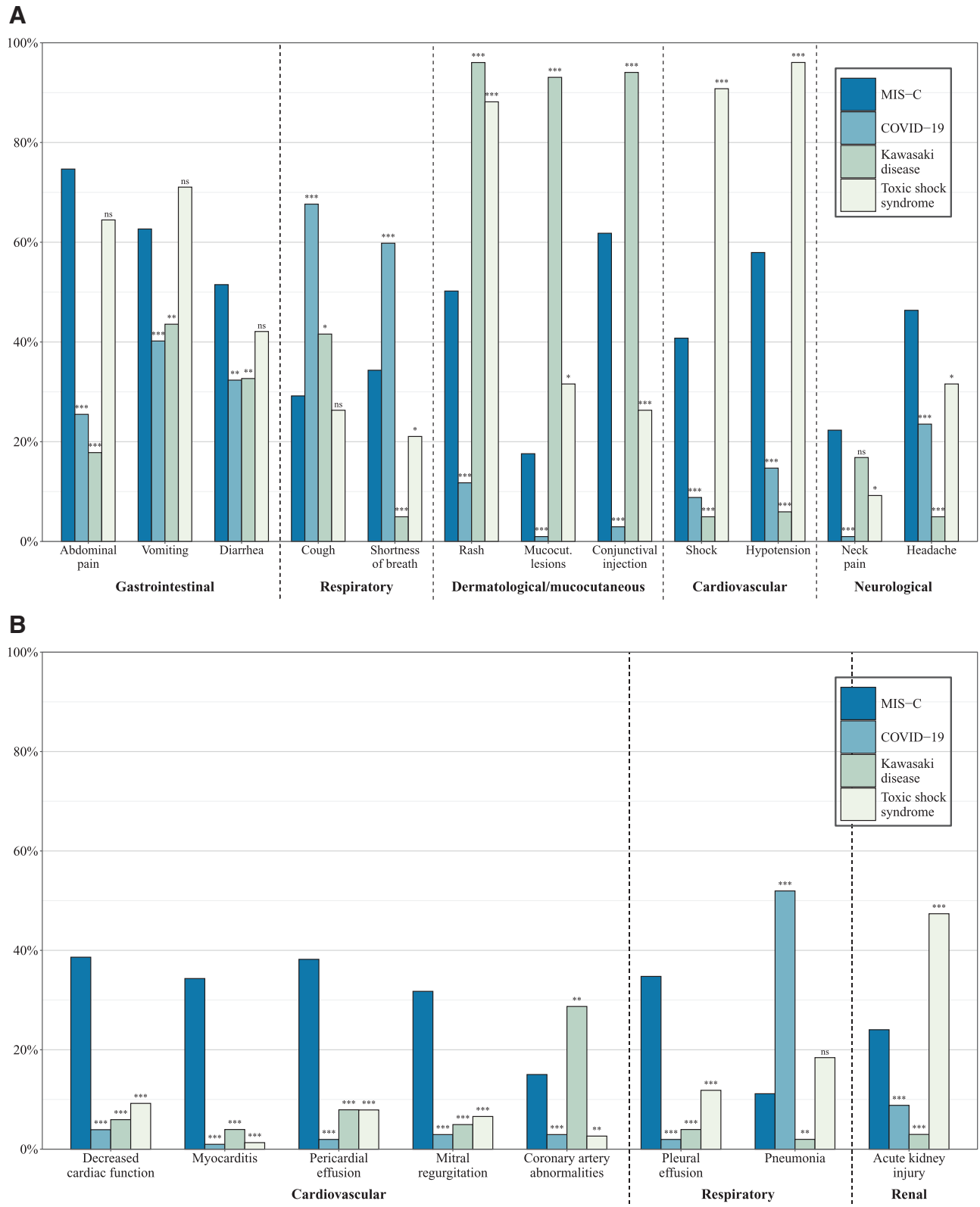


FIGURE 1. Proportions with signs and symptoms and clinical findings of interest for patients with MIS-C, COVID-19, KD, and TSS. Proportions with signs and symptoms (A) and clinical findings (B). *P* values from Fisher exact tests for difference in proportions compared with MIS-C patients denoted as ns (not significant),* ($P < 0.05$), ** ($P < 0.01$), and *** ($P < 0.001$). full color online

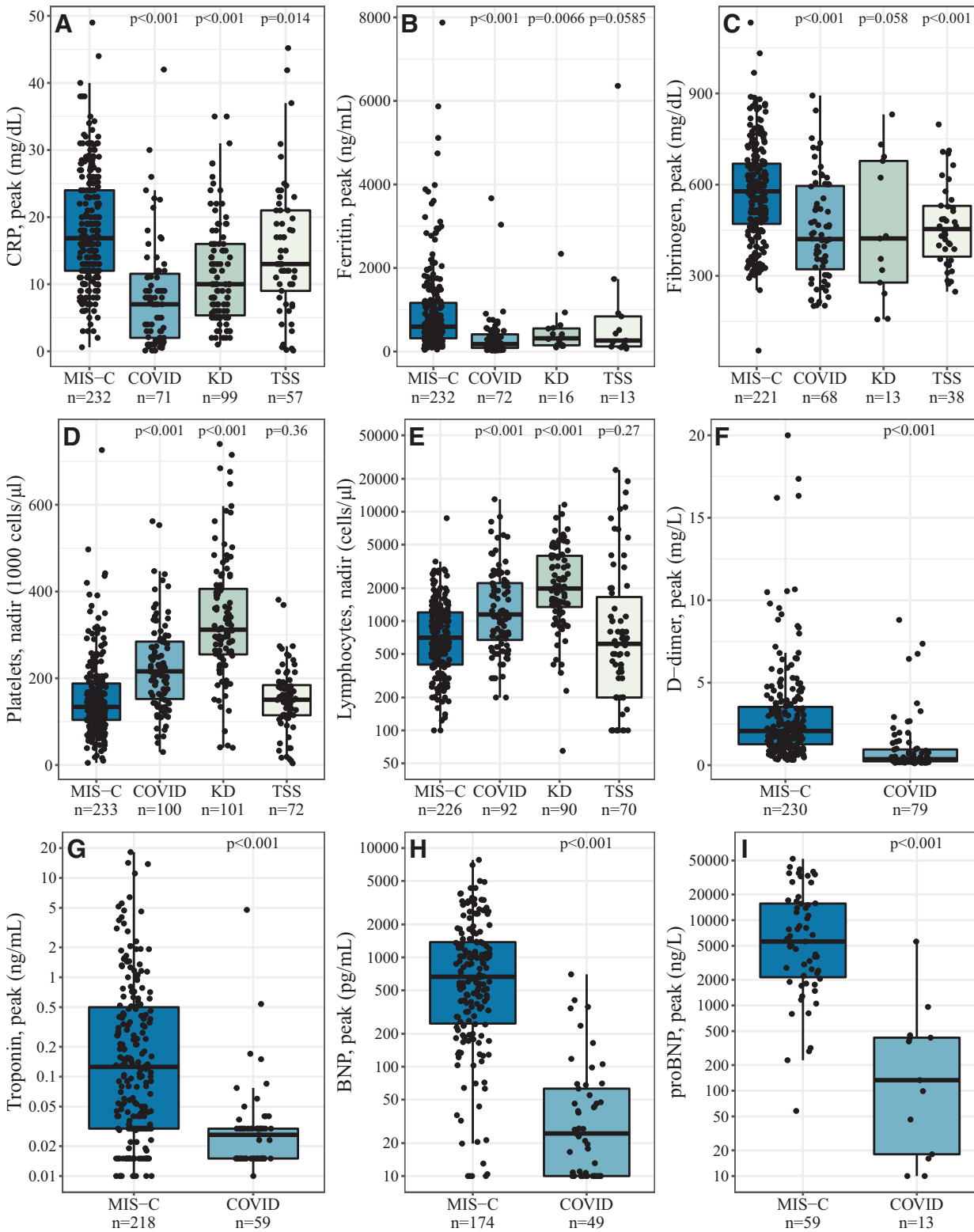
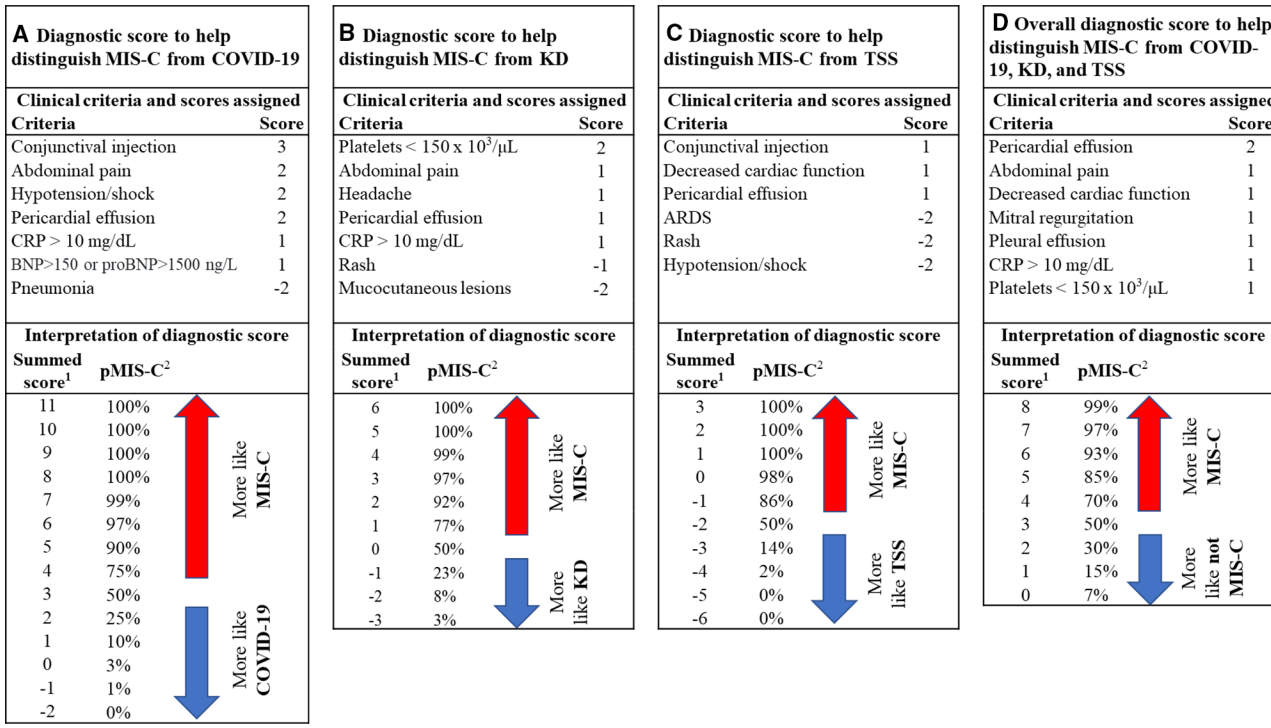


FIGURE 2. Laboratory markers of interest in patients with MIS-C, COVID-19, KD, and TSS. D-dimer, troponin, BNP, and proBNP (panels F-I), do not include comparisons with KD and TSS due to insufficient sample size. full color online



A Diagnostic score to help distinguish MIS-C from COVID-19

Clinical criteria and scores assigned	
Criteria	**Score**
Conjunctival injection	3
Abdominal pain	2
Hypotension/shock	2
Pericardial effusion	2
CRP > 10 mg/dL	1
BNP>150 or proBNP>1500 ng/L	1
Pneumonia	-2

Interpretation of diagnostic score	
Summed score[1]	**pMIS-C[2]**
11	100%
10	100%
9	100%
8	100%
7	99%
6	97%
5	90%
4	75%
3	50%
2	25%
1	10%
0	3%
-1	1%
-2	0%

More like **MIS-C**

More like **COVID-19**

B Diagnostic score to help distinguish MIS-C from KD

Clinical criteria and scores assigned	
Criteria	**Score**
Platelets < 150 x 10^3/μL	2
Abdominal pain	1
Headache	1
Pericardial effusion	1
CRP > 10 mg/dL	1
Rash	-1
Mucocutaneous lesions	-2

Interpretation of diagnostic score	
Summed score[1]	**pMIS-C[2]**
6	100%
5	100%
4	99%
3	97%
2	92%
1	77%
0	50%
-1	23%
-2	8%
-3	3%

More like **MIS-C**

More like **KD**

C Diagnostic score to help distinguish MIS-C from TSS

Clinical criteria and scores assigned	
Criteria	**Score**
Conjunctival injection	1
Decreased cardiac function	1
Pericardial effusion	1
ARDS	-2
Rash	-2
Hypotension/shock	-2

Interpretation of diagnostic score	
Summed score[1]	**pMIS-C[2]**
3	100%
2	100%
1	100%
0	98%
-1	86%
-2	50%
-3	14%
-4	2%
-5	0%
-6	0%

More like **MIS-C**

More like **TSS**

D Overall diagnostic score to help distinguish MIS-C from COVID-19, KD, and TSS

Clinical criteria and scores assigned	
Criteria	**Score**
Pericardial effusion	2
Abdominal pain	1
Decreased cardiac function	1
Mitral regurgitation	1
Pleural effusion	1
CRP > 10 mg/dL	1
Platelets < 150 x 10^3/μL	1

Interpretation of diagnostic score	
Summed score[1]	**pMIS-C[2]**
8	99%
7	97%
6	93%
5	85%
4	70%
3	50%
2	30%
1	15%
0	7%

More like **MIS-C**

More like **not MIS-C**

FIGURE 3. Four diagnostic scores using clinical criteria to help optimally distinguish between MIS-C, COVID-19, KD, and TSS. Panel A: MIS-C and COVID-19, panel B: MIS-C and KD, panel C: MIS-C and TSS, and panel D: MIS-C and COVID-19, KD, and TSS.

The probability calculation assumes a similar number of patients with MIS-C and the other conditions are compared. The following number (and percent) of patients were missing laboratory test results: CRP, 53 (10.3%); lymphocytes, 34 (6.6%); platelets, 6 (1.2%); fibrinogen, 46 (13.7%); troponin, 58 (17.3%); ferritin, 31 (9.3%) and BNP/proBNP, 43 (12.8%). For patients with missing values, multiple imputation was used to determine the likelihood of abnormal lab values. Criteria with negative coefficients indicate that the presence of the criterion decreases the probability that the patient has MIS-C (ie, the absence of the criterion increases the probability that the patient has MIS-C). For a given patient, their plausible diagnoses determine which diagnostic score would be most applicable. [1]The summed score: all criteria that applies to the patient is added together for the total score. [2]pMIS-C is the estimated probability that a patient with each given summed score has MIS-C. ARDS indicates acute respiratory distress syndrome; BNP, brain natriuretic peptide; pMIS-C, probability of MIS-C.

with KD had the highest rates of dermatologic symptoms and the lowest rates of shock, hypotension, respiratory complications, and renal injury. Patients with TSS had the highest rates of shock, hypotension and renal injury.

Case definitions alone were not effective at differentiating MIS-C from COVID-19, KD and TSS; 65%–78% of patients with the latter 3 diseases met the most prominent clinical features included in MIS-C case definition. The utility of SARS-CoV-2 testing in distinguishing these conditions has declined over time as a larger proportion of the population can test positive as a result of natural infection or immunization. Although antinucleoprotein antibody assays can distinguish prior SARS-CoV-2 infection from COVID-19 vaccination, their utility and availability have limitations. Because treatment for each of the conditions can differ, ensuring the correct diagnosis is essential to the provision of rapid and appropriate clinical management. The diagnostic scores summarized in Figure 3 should assist with timeliness and accuracy of diagnosing MIS-C in patients who may have substantial clinical overlap with the other conditions. For example, if a patient was reported to have abdominal pain (2 points), CRP >10 mg/dL (1 point), brain natriuretic peptide >150 ng/L (1 point) and none of the other aforementioned criteria in Figure 3A, the patient is assigned a total score of 4. In a cohort with a roughly equal number of patients with MIS-C and COVID-19, a score of 4 suggests a 75% probability that this patient has MIS-C. If the same patient presents with pneumonia and CRP >10 mg/dL as the only clinical criteria, the total score would be −1, indicating a MIS-C probability of 1% and a likely diagnosis of COVID-19. The diagnostic scores are meant to be a guide for clinicians to assess the likelihood of MIS-C in patients with significant clinical overlap with the other conditions. The variables included in the model are not necessarily components of the case definitions. The diagnostic scores go beyond the case definition to help clinicians evaluate patients' diagnosis based on the totality of available clinical and laboratory data in patients with overlapping features. The diagnostic scores are not intended to assist with determining whether the case meets the MIS-C case definition for reporting purposes.

The findings in this study present similar results to previously published studies comparing MIS-C with KD, KD shock and TSS.[30,31] Patients with MIS-C were more likely to be male and younger in age compared with patients with COVID-19. The racial distribution mirrors that of other published data on MIS-C.[3,5] Overall, patients with KD had the highest percentage of Asian persons and the longest median length of fever. Patients with TSS were more likely to be non-Hispanic White and female; they have the highest rate of intensive care unit admission. Patients with

MIS-C had increased peak levels of CRP compared with patients with COVID-19 and KD and decreased platelets and lymphocyte nadir counts compared with patients with COVID-19 and KD. These laboratory values demonstrate that MIS-C is a highly inflammatory condition with significant cardiac involvement.[30–32] The laboratory values for TSS were not statistically significant except for fibrinogen, which was lower than MIS-C but similar to COVID-19 and KD.

Strengths of the present study include involvement of multicenter sites and utilization of a standardized data collection instrument and chart abstraction for all 4 conditions. Clinical data were abstracted by clinicians from each of the 4 hospitals, and abstractors had direct access to medical records. Although the diagnostic scores were internally validated and were successful at distinguishing MIS-C from the other disease categories, future external validation using different sets of patients can improve their application. The diagnostic scores can potentially be integrated into electronic health records for ease of implementation.

The study has several limitations. First, the 4 institutions are in geographically distinct locations, but the majority of KD patients were identified from a single location, potentially decreasing the racial, ethnic and geographic diversity. However, data from patients with MIS-C, COVID-19 and TSS were provided by all 4 partnering hospitals, which improves the diversity of patient data. Second, the case report form did not include details for some of the variables, such as type of neck pain. Third, because of the retrospective data collection, clinical and laboratory data may not have been consistently collected or recorded in the medical records. For instance, troponin was not routinely tested in most patients with KD and TSS; it was often elevated in MIS-C but not typically in KD.[4,33] Lastly, serial test results were unavailable; only the highest and lowest laboratory values were collected. In previous studies, the most abnormal values are generally recorded at or shortly after illness presentation, indicating that those values closely approximate laboratory findings early in the course of hospitalization when patient diagnosis is most critical.[34,35]

CONCLUSION

MIS-C can be challenging to differentiate from COVID-19 and other hyperinflammatory conditions. Patients with a history of SARS-CoV-2 infection or positive serology for SARS-CoV-2 who present with gastrointestinal and cardiac dysfunction, elevated markers of inflammation and significantly elevated cardiac markers are more likely to have MIS-C than patients with respiratory symptoms requiring noninvasive respiratory support. Patients with KD typically have a lower median age, more often have mucocutaneous lesions and coronary artery abnormalities, and less frequently have cardiac dysfunction and myocarditis. Patients with TSS were more likely to be non-Hispanic White and female with shock and hypotension and low rates of cardiovascular complications. In patients with substantial overlap in clinical manifestation, the diagnostic scores can be a valuable tool for distinguishing MIS-C from COVID-19, KD and TSS.

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16. § See e.g., 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.
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Current Abstracts

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Bloodstream Infections in Children With Sickle Cell Disease: 2010–2019

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Children with sickle cell disease (SCD) are at increased risk for bloodstream infections (BSIs), particularly with encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. This infection risk is related to impaired or absent splenic function, other immune defects, and anatomic predisposition as occurs with osteomyelitis. The placement of a central venous catheter (CVC) also increases the risk of BSI. The Cooperative Study of Sickle Cell Disease, which was conducted in an era before routine penicillin prophylaxis or pneumococcal immunizations, provided a prospective longitudinal assessment of bacteremia risk, revealing that incidence rates were highest in patients with hemoglobin SS <3 years of age and decreased with age during the first 2 decades of life, predominantly because of *S. pneumoniae* and *H. influenzae*. Later retrospective studies from 1993 to 2010 demonstrated *S. pneumoniae*, *Salmonella*, *Escherichia coli,* and *Staphylococcus aureus* as causes of bacteremia in SCD.

Large-scale studies of BSI in children with SCD in the current era are needed to understand the contemporary infection risk, guide empirical antibiotic therapy during febrile episodes, and guide policy decisions for targeted immunization schedules. The aims of this study were to determine the annual incidence and associated features of BSI in children with SCD in a large health care system over a 10-year period from 2010 to 2019 and to delineate the specific microorganisms responsible for BSI in this era.

A retrospective cohort study to review all blood cultures from children <18 years of age with SCD obtained at Children's Healthcare of Atlanta (CHOA) in Atlanta, Georgia, from January 1, 2010 to December 31, 2019 was conducted. CHOA is the primary pediatric health care system in the metropolitan region, with 3 academic hospitals that provide outpatient, emergency, and inpatient care to the majority (>95%) of children with SCD in the Atlanta metropolitan area.

In the 10-year period, which captured 3624 patients with SCD, 2694 (74.3%) patients with a total of 19,902 blood cultures met inclusion criteria. When repeat blood cultures were excluded, there remained 15,208 unique cultures. After exclusion of positive culture results from presumed contaminant growth (n = 168 cultures), there were 156 episodes of BSI (1.0% of blood cultures) among 144 patients. For BSI, the blood culture sources were peripheral blood in 123 and CVC in 33 (21.1%). The mean age was slightly older for those with positive versus negative blood culture results (8.4 vs. 7.5 years, $P = 0.49$). BSIs were more prevalent in patients with a sickle cell anemia (SCA) genotype (hemoglobin SS or $SBeta^0$ thalassemia) versus a non-SCA genotype (hemoglobin SC or $SBeta^+$ thalassemia) and patients on chronic transfusion therapy. Among BSI episodes, 25 (16.0%) occurred in patients with splenectomy, and 78 (50.0%) occurred in patients on antibiotic prophylaxis (71 on penicillin, 4 on amoxicillin, 3 on other). Treatment with hydroxyurea revealed a significant risk reduction in multivariate analysis.

The average annual incidence of BSI over the 10-year period was 0.89 per 100 person-years [95% confidence interval (CI): 0.45–1.32]. The incidence rate for children <5 years was 1.42 per 100 person-years (95% CI: 0.31–2.52) compared with an incidence rate of 0.78 per 100 person-years (95% CI: 0.29–1.26) for children ≥ 5 years. The most prevalent pathogen was *S. pneumoniae* (n = 25, 16% of BSIs), followed by *Staphylococcus* (n = 12 for *S. aureus*, n = 5 for *S. epidermidis*, n = 3 for other coagulase-negative *Staphylococcus*) and *Streptococcus* (n = 23 viridans group, n = 1 *Streptococcus pyogenes*). Prevalent Gram-negative organisms included *E. coli* (n = 14, 9.0%), *Bordetella holmesii* (n = 12, 7.7%), *H. influenzae* (n = 11, 7.1%) and *Salmonella* species (n = 10, 6.4%). *H. influenzae* included serotypes f (n = 6) and a (n = 1) and nontypeable *H. influenzae* (n = 3) and was not tested in 1 case.

Serotypes of *S. pneumoniae* isolates were determined for 24 of 25 cases. Pneumococcal BSI occurred in 7 (25%) children <24 months of age, in 7 (28%) children 24 to 59 months of age, and in 11 (44%) ≥ 60 months of age. There were 12 (48%) isolates of serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (10A, 12F, 15B/C, 22F). No serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13) were isolated. Among children who had a PPSV23 serotype, 6 (50%) had received at least one PPSV23 immunization (5 with one dose, 1 with two doses), whereas among children with a non-PPSV23 serotype, 9 (75%) had at least one PPSV23 immunization ($P = 0.20$).

Antimicrobial susceptibility was available for select pathogens. For *S. pneumoniae*, all isolates tested (n = 23) revealed susceptibility to ceftriaxone at both non-meningitis (<1 μg/mL) and meningitis (≤0.5 μg/mL) breakpoints and to penicillin at non-meningitis breakpoints. However, only 61% were susceptible to penicillin at the meningitis breakpoint.

There were 14 deaths within the study inclusion cohort: 3 deaths during illnesses associated with a BSI and 11 deaths during which blood culture results at CHOA were negative. Two deaths were attributable to *S. pneumoniae* sepsis and one death in a patient with CVC-associated BSI (methicillin-resistant *S. aureus*).

Comment: Although infection and its associated mortality have decreased substantially over the past decades, children with SCD remain at risk for BSI, particularly those with SCA genotypes or a CVC. The findings of this study continue to inform clinical practices for immunization, including the recently FDA-approved (for adults 18 years and older) conjugate pneumococcal vaccines PCV 15 and PCV 20.