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Emergency department screening for multisystem inflammatory syndrome (MIS-C) in children

1. Introduction

Multisystem inflammatory syndrome in children (MIS-C) was defined by the Centers for Disease Control and Prevention (CDC) in May 2020 [1]. An approach to the identification of this uncommon yet life-threatening illness among well-appearing febrile children presenting for medical care is urgently needed as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continuous to affect millions worldwide [2,3]. Thus, the aims of this report are to: (1) describe our institutional approach to screening for MIS-C; (2) report the test characteristics of our approach in excluding MIS-C; and (3) provide recommendations for screening for MIS-C among well appearing children with fever.

2. Methods

Screening for MIS-C at an urban, tertiary care pediatric emergency department (PED) located in a geographic area with a high burden of SARS-CoV-2 infections [2] was implemented on May 7, 2020. For well appearing children presenting with fever ≥48 h with rash, gastrointestinal symptoms, or clinical features of Kawasaki Disease [4], the initial recommended screening laboratory studies include: complete blood count with differential (CBC), comprehensive metabolic panel (CMP), C-reactive protein (CRP), ferritin, d-dimer, and high-sensitivity troponin I (troponin). We retrospectively reviewed the PED logs for May 7 to May 31, 2020 to identify patients <21 years of age with a relevant chief complaint (e.g. fever, diarrhea, rash) who had a ferritin, d-dimer or troponin performed (as CBC, CMP, and CRP are not specific to our screening algorithm). Demographic and clinical characteristics, including final diagnoses, and laboratory values were abstracted by clinicians using a standardized data collection tool and entered into Research Electronic Data Capture (REDCap) [5].

For analysis, patients were dichotomized as MIS-C or not (see Table 1). Means/standard deviations, medians/interquartile ranges, or frequencies/95% confidence intervals (CI) were calculated for patient characteristics. Univariate logistic regression (LR) was used to assess the association of clinical data with the primary outcome (non-MIS-C); those with $p < 0.1$ were assessed for independent association using multivariable LR. Co-linearity of predictors was assessed using variance inflation factor. As our goal was to identify characteristics associated with a low probability of MIS-C, composite predictor variables were created, with candidates selected from the multivariable analysis or "by meaning". Continuous predictors (except age) were dichotomized with a cut-point determined by Youden's J statistic. Meeting institutional or CDC clinical criteria for screening was also included in the composite variable. Final model selection was based on comparison of Akaike's Information Criteria, area under the receiver operating characteristic curve (AUC), and CI width (narrower considered more clinically informative). Two-tailed significance level was set at 0.05. Statistical analysis was performed using SAS v9.4 (Cary, NC).

3. Results

Among 2536 patients presenting during the study period, 196 (8%) were included in the analysis and 12 (0.5%) were categorized as MIS-C. Demographics and screening laboratory results are reported in Table 1. On multivariable analysis, troponin, d-dimer, ferritin, CRP, and age had significant inverse associations with the primary outcome. Composite laboratory value predictor variables performed differently depending on whether institutional or CDC clinical screening criteria were used. Final models for each, along with independent contribution of age, are presented in Table 2.

4. Conclusions

Although limited by sample size, this timely report is the first to provide clinicians with a preliminary approach to screening febrile children for MIS-C. While larger validation studies are needed, children meeting the CDC clinical criteria [1] should have a CRP, troponin, and ferritin performed. Patients with results below the identified cut-points are at lower risk for MIS-C and can be discharged home with close primary care follow-up. Given its association with greater likelihood of disease, increased age should be incorporated into clinical decision making among children being screened for MIS-C.

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Contributors statement

DeLaroche - conceptualization, data curation, project administration, software supervision, validation, writing - original draft, writing - review and editing. Stankovic & Ruffing: conceptualization, data curation, writing - review and editing. Ehrman - formal analysis, writing - original draft, writing - review and editing. Noble, Arora, Maksimowski - data curation, writing - review and editing.

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article to disclose.

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Table 1
Demographic and clinical characteristics of the study cohort

Characteristic	All Cases	Non MIS-C	MIS-C*
	$n = 196$	$n = 184$	$n = 12$
Demographics, *n* (%)			
Age, median (IQR), years	2.0 (6.0)	1.5 (6.0)	8.5 (6.5)
Female gender	103 (53)	94 (51)	9 (75)
Race			
Caucasian	48 (25)	46 (25)	2 (17)
African-American	95 (49)	88 (48)	7 (58)
Other	53 (27)	50 (27)	3 (25)
Index visit	167 (85)	159 (86)	8 (67)
PED Disposition			
Admission	129 (66)	117 (64)	12 (100)
Discharge	67 (34)	67 (36)	0 (0)
PICU admission during hospitalization	20 (16)	10 (9)	10 (83)
Presenting Clinical Features by System, *n* (%)			
Fever§	182 (93)	171 (93)	11 (92)
Respiratory	78 (40)	71 (39)	7 (58)
Gastrointestinal	163 (83)	152 (83)	11 (92)
Neurological	23 (12)	17 (9)	6 (50)
Cardiac	12 (6)	11 (6)	1 (8)
Musculoskeletal	13 (7)	12 (7)	1 (8)
Mucocutaneous	78 (40)	71 (39)	7 (58)
Screening Laboratory Study Results, median (IQR)			
White blood cell count (reference range: 4.1–10.1 $\times$ 10^9/L)	8.50 (6.50) [195]	8.40 (6.40) [183]	10.95 (8.70) [12]
Neutrophil count (reference range: 1.58–7.13 $\times$ 10^9/L)	4.20 (5.50) [190]	4.00 (5.20) [178]	9.00 (7.20) [12]
Lymphocyte count (reference range: 0.8–5.0 $\times$ 10^9/L)	2.50 (2.90) [190]	2.70 (3.10) [178]	1.05 (0.70) [12]
Hemoglobin (reference range: 11.7–15.9 g/dL)	11.90 (1.40) [195]	11.90 (1.30) [183]	11.35 (1.90) [12]
Platelet count (reference range: 130–450 $\times$ 10^9/L)	260 (119) [194]	262 (113) [182]	202 (216) [12]
CRP (reference range: <5.0 mg/L)	14.65 (63.90) [194]	11.55 (52.90) [182]	139.65 (76.55) [12]
Ferritin (reference range: 11.0–306.8 μg/L)	73.40 (93.50) [191]	70.80 (83.80) [179]	318.15 (418.25) [12]
Albumin (reference range: 3.8–5.1 g/dL)	4.40 (0.50) [192]	4.40 (0.40) [180]	3.90 (0.75) [12]
ALT (reference range: 7–52 U/L)	17.00 (12.00) [192]	17.00 (12.00) [180]	17.50 (45.00) [12]
Troponin I, high sensitivity (reference range: 3–17 ng/L)	7.00 (7.00) [194]	7.00 (6.00) [182]	36.50 (97.00) [12]
D-dimer (reference range: <0.50 mg/L FEU)	0.71 (0.87) [189]	0.69 (0.79) [177]	1.95 (1.60) [12]

Abbreviations: ALT, alanine aminotransferase; CRP, C-reactive protein; PED, pediatric emergency department; PICU, pediatric intensive care unit; FEU, fibrinogen equivalent units; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
SI conversion factors: To convert hemoglobin to g/L multiply by 10; to convert albumin to g/L multiply by 10; to convert ALT to μkat/L multiply by 0.0167.
Two patients with MIS-C met CDC criteria except for laboratory confirmed SARS-CoV-2 infection or an epidemiological link to SARS-CoV-2. One patient with MIS-C met CDC criteria except for fever, which was absent at home but had reported chills at home and a documented fever in the PED.
* Patients included in the MIS-C group had a presumptive diagnosis of MIS-C early in their hospital course made by a specialist in pediatric infectious disease and all were treated with intravenous immunoglobulin. Final discharge diagnoses were MIS-C (11) and hemophagocytic lymphohistiocytosis (1). Eight patients with MIS-C met CDC criteria.
§ Fever included subjective or documented fever prior to PED arrival.

Table 2
OR, AUC, sensitivity, and specificity of screening algorithms for the exclusion of MIS-C among pediatric patients presenting to the PED

Algorithm	OR	95% CI	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Age# OR (95% CI)
A. CDC clinical criteria* met plus composite laboratory criteria 1§	17.44	3.67–82.75	0.81 (0.69–0.92)	0.78 (0.72–0.84)	0.83 (0.62–1.00)	0.86 (0.76–0.97)
B. Institutional clinical criteria¥ met plus composite laboratory criteria 2^	19.65	5.35–72.08	0.78 (0.65–0.93)	0.91 (0.87–0.95)	0.67 (0.40–0.93)	0.87 (0.77–0.99)
C. CDC clinical criteria* met plus compisite laboratory criteria 2^	60.71	12.10–304.66	0.88 (0.77–0.99)	0.92 (0.89–0.96)	0.83 (0.62–1.00)	0.91 (0.79–1.04)
D. Institutional clinical criteria¥ met plus composite laboratory criteria 1§	5.83	1.68–20.25	0.71 (0.56–0.85)	0.74 (0.68–0.81)	0.67 (0.40–0.93)	0.84 (0.75–0.95)

Abbreviations: AUC, area under the curve; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CRP, c-reactive protein; PED, pediatric emergency department; MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio.
* CDC clinical criteria defined as fever ≥24 h plus ≥2 systems involved at the time of PED presentation.
§ Lab criteria 1: CRP & high-sensitivity Troponin I & ferritin all above cut-points, defined as CRP ≥ 87.5 mg/L; troponin *I* ≥ 17 ng/L; ferritin ≥121.6 ng/mL.
¥ Institutional clinical criteria defined as fever ≥48 h plus one of the following: gastrointestinal features (abdominal pain, vomiting, diarrhea), mucocutaneous features (rash, conjunctivitis, erythema of oral/pharyngeal mucosa), or lymphadenopathy.
^ Lab criteria 2: [CRP & d-dimer & ferritin] OR troponin I above the optimal cut-point, defined as CRP ≥ 87.5 mg/L; troponin I, high sensitivity ≥17 ng/L; ferritin ≥121.6 ng/mL; d-dimer ≥1.07 mg/L fibrinogen equivalent units (FEU).
# Effect per 1 year increase in age when added to corresponding clinical/laboratory model.

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