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Predictors of severe illness in children with multisystem inflammatory syndrome after SARS-CoV-2 infection: a multicentre cohort study

Michelle Barton-Forbes, *Western University*

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Predictors of severe illness in children with multisystem inflammatory syndrome after SARS-CoV-2 infection: a multicentre cohort study

Joanna Merckx MD, Suzette Cooke MD PhD, Tala El Tal MD, Ari Bitnun MD, Shaun K. Morris MD, E. Ann Yeh MD, Carmen Yea MSc, Peter Gill MD, Jesse Papenburg MD, Marie-Astrid Lefebvre MD, Rosie Scuccimarri MD, Rolando Ulloa-Gutierrez MD, Helena Brenes-Chacon MD, Adriana Yock-Corrales MD, Gabriela Ivankovich-Escoto MD, Alejandra Soriano-Fallas MD, Marcela Hernandez-de Mezerville MD, Tammie Dewan MD, Lea Restivo MD, Alireza Nateghian MD, Behzad Haghighi Aski MD, Ali Manafi MD, Rachel Dwilow MD, Jared Bullard MD, Alison Lopez MD, Manish Sadarangani MD, Ashley Roberts MD, Michelle Barton MD, Dara Petel MD, Nicole Le Saux MD, Jennifer Bowes MD, Rupeena Purewal MD, Janell Lautermilch MD, Sarah Tehseen MD, Ann Bayliss MD, Jacqueline K. Wong MD, Kirk Leifso MD, Cheryl Foo MD MPH, Joan Robinson MD; for the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC)

Abstract

Background: SARS-CoV-2 infection can lead to multisystem inflammatory syndrome in children (MIS-C). We sought to investigate risk factors for admission to the intensive care unit (ICU) and explored changes in disease severity over time.

Methods: We obtained data from chart reviews of children younger than 18 years with confirmed or probable MIS-C who were admitted to 15 hospitals in Canada, Iran and Costa Rica between Mar. 1, 2020, and Mar. 7, 2021. Using multivariable analyses, we evaluated whether admission date and other characteristics were associated with ICU admission or cardiac involvement.

Results: Of 232 children with MIS-C (median age 5.8 yr), 130 (56.0%) were male and 50 (21.6%) had comorbidities. Seventy-three (31.5%) patients were admitted to the ICU but none died. We observed an increased risk of ICU admission among children aged 13–17 years (adjusted risk difference 27.7%, 95% confidence interval [CI] 8.3% to 47.2%), those aged 6–12 years (adjusted risk difference 25.2%, 95% CI 13.6% to 36.9%) or those with initial ferritin levels greater than 500 µg/L (adjusted risk difference 18.4%, 95% CI 5.6% to 31.3%). Children admitted to hospital after Oct. 31, 2020, had numerically higher rates of ICU admission (adjusted risk difference 12.3%, 95% CI –0.3% to 25.0%) and signifi-

cantly higher rates of cardiac involvement (adjusted risk difference 30.9%, 95% CI 17.3% to 44.4%). At Canadian sites, the risk of ICU admission was significantly higher for children admitted to hospital between December 2020 and March 2021 than those admitted between March and May 2020 (adjusted risk difference 25.3%, 95% CI 6.5% to 44.0%).

Interpretation: We observed that age and higher ferritin levels were associated with more severe MIS-C. We observed greater severity of MIS-C later in the study period. Whether emerging SARS-CoV-2 variants pose different risks of severe MIS-C needs to be determined.

Multisystem inflammatory syndrome in children (MIS-C)[1] manifests as immune dysregulation after SARS-CoV-2 infection.[2] The syndrome has no pathognomonic features. Thus, the diagnostic criteria of the Royal College of Paediatrics and Child Health (RCPCH), the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) differ, but they all include

fever, evidence of systemic inflammation and involvement of at least 1 organ or system.[3]

Our primary objective was to assess initial clinical or laboratory features that predict severe illness in MIS-C. We also sought to explore changes in overall disease severity and cardiac involvement over time as it was the impression of many investigators that severity of MIS-C increased through pandemic waves.

Methods

This was part of a larger study. Investigators from 15 pediatric hospitals (13 in Canada and 1 each in San José, Costa Rica, and Tehran, Iran; Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content) included consecutive children aged younger than 18 years who were admitted to hospital from Mar. 1, 2020, through Mar. 7, 2021, and who fulfilled the WHO criteria for MIS-C, namely fever (not otherwise defined) for at least 3 days; elevated C-reactive protein, erythrocyte sedimentation rate or procalcitonin level; illness involving 2 or more systems, with no other obvious microbial cause of inflammation; and "evidence of COVID-19 ([reverse transcription polymerase chain reaction], antigen test or serology positive [for SARS-CoV-2 infection]), or likely contact with patients with COVID-19."[4] Given that asymptomatic individuals can transmit SARS-CoV-2,[5] any child residing in a community with ongoing SARS-CoV-2 transmission was considered to have "likely contact." In addition, we included patients who otherwise fulfilled WHO criteria but had fever for less than 3 days, if they received corticosteroids or intravenous immunoglobulin (IVIG) as treatment for MIS-C before the third day of fever. We excluded patients with a likely alternative diagnosis. We identified cases by screening admission lists, reviewing charts of children admitted to hospital with positive SARS-CoV-2 test results and communicating with the clinical services likely to admit or be consulted on MIS-C cases.

Co-investigator physicians (11 sites) or their supervised research assistants (4 sites) collected study data using REDCap electronic data capture tools, hosted at the University of Alberta. We used chart review to collect primary reason for admission, demographics, comorbidities, clinical presentation and course, coinfections, treatments and complications (Appendix 1). We designed the initial case report form for acute SARS-CoV-2 cases and continually modified it over time to clarify any confusing questions. Multisystem inflammatory syndrome in children was not described when the study started, so the MIS-C questions were added in May 2020. If investigators were aware of patients who met the MIS-C criteria and were admitted before May 2020, they entered them once the MIS-C questions were added.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[6]

Definitions

We considered patients to have confirmed MIS-C if, in addition to fulfillment of MIS-C clinical criteria, SARS-CoV-2 or antibodies to SARS-CoV-2 were detected at any point. We considered patients to have probable MIS-C if they fulfilled MIS-C clinical criteria but SARS-CoV-2 tests were negative or not performed. Definitions of other clinical manifestations of SARS-CoV-2 infection are shown in Appendix 2, Supplementary Table 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content.

Outcomes

Our outcomes were hospital length of stay, need for intensive care unit (ICU) admission and cardiac involvement. As criteria for ICU admission varied by site, we assessed a "critical disease" outcome (defined as ICU admission with use of vasopressors, or noninvasive or mechanical ventilation) in a sensitivity analysis.

Statistical analysis

We used descriptive statistics to compare demographic, clinical, laboratory and treatment data, as well as outcomes to identify differences between patients with confirmed and probable SARS-CoV-2 infections and between the participating countries. We analyzed categorical data using the χ^2 or Fisher exact test and analyzed continuous data using the Kruskal–Wallis test for medians.

We used multivariable logistic or linear log-transformed regression analysis, as appropriate, to explore clinical and laboratory factors at hospital admission, and their association with outcomes. We assessed factors of interest in separate multivariable models, including age, sex, country, initial ferritin, leukocyte count, platelet count and organ system involvement on admission. We created a directed acyclic graph to inform the assessment of potential confounders, mediators and colliders for the outcome variables, and to sequentially build the models (Appendix 3, Supplementary Figure 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content).[7] Rates of missing data in the included variables were low (< 4%) and we excluded missing data from the analysis. We assessed model fit using the Hosmer–Lemeshow goodness-of-fit test for logistic and R^2 for linear regression. We also investigated potential overfitting (Appendix 4, Supplementary Methods, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content). We reported results of regression models as adjusted predicted probabilities of the outcome (absolute risks and risk differences) representing the average marginal effect across the total study population.[8] We considered a risk difference that did not include the null (0%) in its confidence interval (CI) as statistically significant.

To evaluate temporal changes in severity, we compared outcomes for 2 time cohorts, Mar. 1–Oct. 31, 2020, and Nov. 1, 2020–Mar. 7, 2021, analyzing time as an exposure in separate explorative models. We arbitrarily chose these dates before data analysis to divide the cases into roughly equal groups. It was not possible to analyze cases by epidemic wave, as distinct waves did not occur in Costa Rica. We analyzed data from Canada separately for risk factors of ICU admission and cardiac involvement, dividing cases into 3-month periods from March 2020 (adding the 3 patients admitted to hospital in March 2021 to the fourth quarter). In addition, we used a sensitivity analysis to compare outcomes for confirmed and probable cases. We did not make adjustments for multiple comparisons.

We analyzed data using STATA 13 (StataCorp. College Station).

Ethics approval

The study was approved by the research ethics boards at the University of Alberta (Pro00099426) and all participating sites.

Results

We included 232 children with MIS-C (106 confirmed, 126 probable) (Figure 1), of whom 130 (56.0%) were male and 50 (21.6%) had 1 or more comorbidities. The median age of patients was 5.8 (interquartile range [IQR] 3.0–9.5) years. Figure 2 shows the number of patients with MIS-C over time, in relation to the regional average number of COVID-19 cases. Data by country is in Appendix 2, Supplementary Table 2.

Patients who initially met WHO MIS-C criteria
n = 239

Excluded: other primary diagnosis considered to be more likely
by treating clinician *n* = 7
• Epstein–Barr infection *n* = 2
• Osteomyelitis *n* = 1
• Serum sickness *n* = 1
• Hemophagocytic lymphocytic histiocytosis *n* = 1
• Ruptured Meckel diverticulum *n* = 1
• Urinary tract infection *n* = 1

Proven cases *n* = 106
• Serology positive, SARS-CoV-2 detected *n* = 26
• Serology not performed, SARS-CoV-2 detected *n* = 28
• Serology negative, SARS-CoV-2 detected *n* = 6
• Serology positive, SARS-CoV-2 not detected *n* = 44
• Data missing *n* = 2

Probable cases *n* = 126
• Serology negative, SARS-CoV-2 not detected *n* = 81
• Serology not performed, SARS-CoV-2 not detected *n* = 39
• Data missing *n* = 6

Figure 1: Flowchart of study inclusion of patients admitted to hospital with confirmed or probable multisystem inflammatory syndrome in children (MIS-C). Note: WHO = World Health Organization.
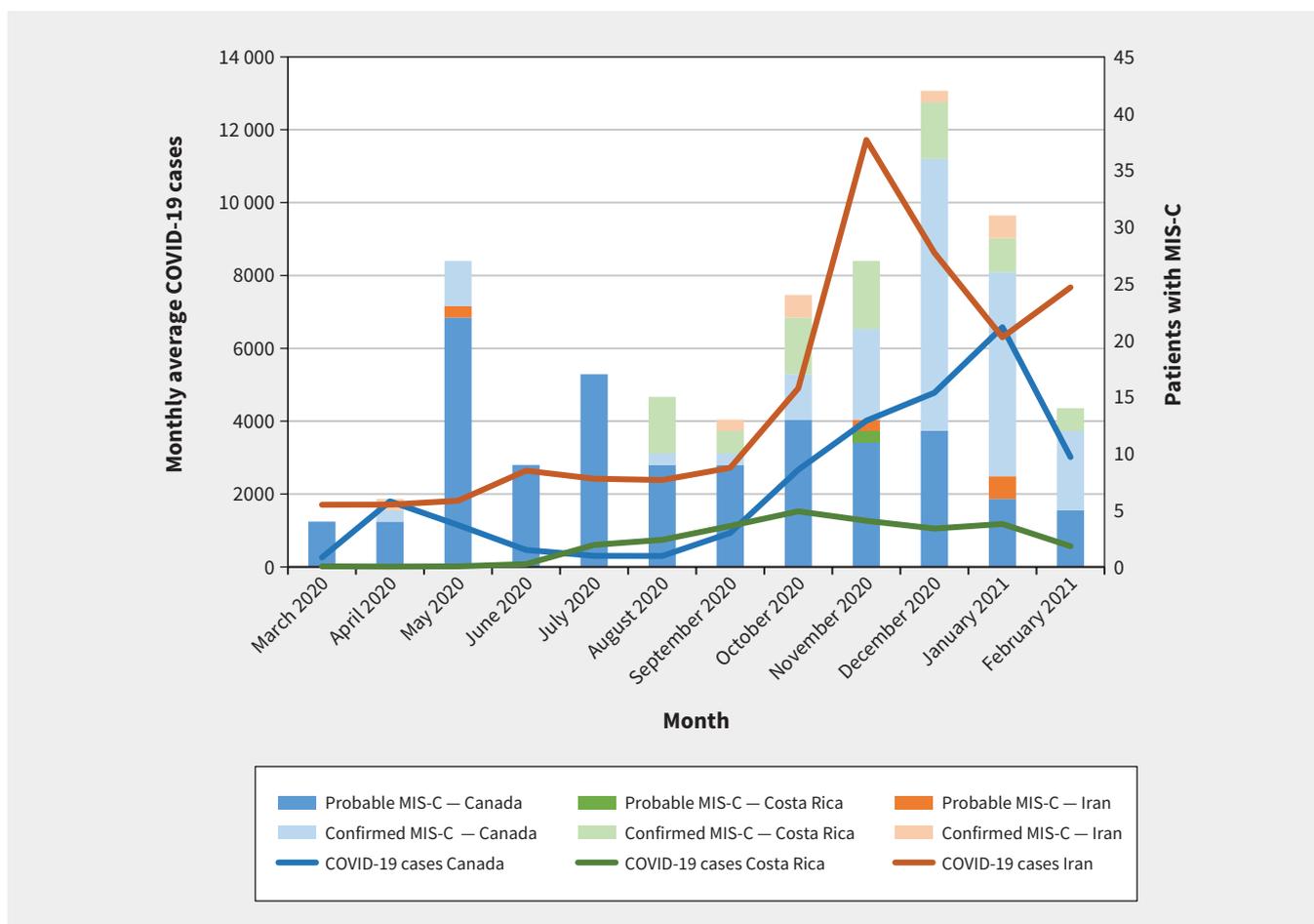
Figure 2: Patients with multisystem inflammatory syndrome in children (MIS-C) in Canada, Costa Rica and Iran from Mar. 1, 2020, and Mar. 7, 2021 (patients admitted in March 2021 included in February 2021 counts). Monthly COVID-19 case counts are averaged over the 5th, 15th and 25th of the month (https://coronavirus.jhu.edu/map.html).

Table 1 (part 1 of 2): Characteristics of patients admitted to hospital with multisystem inflammatory syndrome in children from Mar. 1, 2020, to Mar. 7, 2021

Characteristic	No. (%) of patients*		
	Confirmed MIS-C $n = 106$	Probable MIS-C $n = 126$	All cases $n = 232$
Age, yr, median (IQR)	6.85 (4.01–9.66)	4.93 (1.92–8.87)	5.75 (3.02–9.49)
Age categories, yr			
0–5	46 (43.3)	74 (58.7)	120 (51.7)
6–12	48 (45.3)	40 (31.7)	88 (37.9)
13–18	12 (11.3)	12 (9.5)	24 (10.3)
Sex, male	61 (57.5)	69 (54.8)	130 (56.0)
Country			
Canada	69 (65.1)	121 (96.0)	190 (81.9)
Costa Rica	29 (27.4)	1 (0.8)	30 (12.9)
Iran	8 (7.5)	4 (3.2)	12 (5.2)
≥ 1 comorbidities†‡	22 (20.8)	28 (22.2)	50 (21.6)
Duration of fever before admission, d, median (IQR)§	4 (3–5)	5 (3–6)	4 (3–6)
Total duration of fever, d, median (IQR)§	6 (4–8)	7 (6–10)	6 (5–9)
Mucocutaneous signs¶	89 (84.0)	107 (84.9)	196 (84.5)
Gastrointestinal involvement**	100 (94.3)	107 (84.9)	207 (89.2)
Cardiac involvement††	81 (76.4)	55 (43.7)	136 (58.6)
Echocardiogram performed	102 (96.2)	124 (98.4)	226 (97.4)
Normal or changes not compatible with MIS-C	52 (49.1)	83 (65.9)	135 (58.2)
Changes compatible with MIS-C‡‡	50 (47.2)	40 (31.7)	90 (38.8)
Coronary artery z score ≥ 2.5	5 (4.7)	15 (11.9)	21 (9.1)
Abnormal coronary arteries§§	17 (16.0)	8 (6.3)	25 (10.8)
Coronary artery aneurysm	1 (0.9)	1 (0.8)	2 (0.9)
Ascending aorta dilatation	1 (0.9)	7 (5.6)	8 (3.4)
Poor systolic function	20 (18.9)	6 (4.8)	26 (11.2)
Regurgitation of ≥ 1 valves	18 (17.0)	6 (4.8)	24 (10.3)
Myocarditis	2 (1.9)	3 (2.4)	5 (2.2)
Pericardial effusion	10 (9.4)	6 (4.8)	16 (6.9)
Bundle branch block	0 (0)	1 (0.8)	1 (0.4)
Prolonged Q-T interval	1 (0.9)	0 (0)	1 (0.4)
Possible thrombus in ventricle	0 (0)	1 (0.8)	1 (0.4)
NT-ProBNP or troponins elevated, despite no evidence of cardiac involvement on echocardiogram	31 (29.2)	15 (11.9)	46 (19.8)
Abnormal coagulation profile¶¶	103 (97.2)	106 (84.1)	209 (90.1)
Neurological complications	5 (4.7)	4 (3.2)	9 (3.9)
Clinical hematological complications***	1 (0.9)	2 (1.6)	3 (1.3)
Contact with a person with proven SARS-CoV-2 infection	42 (39.6)	8 (6.3)	50 (21.6)
Bacterial coinfection	2 (1.9)	10 (7.9)	12 (5.2)
Viral coinfection	6 (5.7)	3 (2.4)	9 (3.9)
Laboratory results			
Peak C-reactive protein, mg/L, median (IQR)	145 (89–206)	122 (67–203)	135 (83–204)
Ferritin, μg/L			
Not measured	3 (2.8)	4 (3.2)	7 (3.0)
Initial value, median (IQR)	367 (208–649)	207 (114–404)	265 (144–482)
Peak value, median (IQR)	463 (284–835)	259 (122–555)	376 (173–689)

Table 1 (part 2 of 2): Characteristics of patients admitted to hospital with multisystem inflammatory syndrome in children from Mar. 1, 2020, to Mar. 7, 2021

Characteristic	No. (%) of patients*		
	Confirmed MIS-C $n = 106$	Probable MIS-C $n = 126$	All cases $n = 232$
Initial leukocyte count, × 10⁹/L, median (IQR)	11.6 (7.8–15.0)	9.2 (6.5–12.8)	10.6 (7.0–14.4)
Lowest neutrophil count, × 10⁹/L, median (IQR)	3.6 (2.5–5.7)	2.7 (1.4–4.3)	3.1 (1.8–4.8)
Highest neutrophil count, × 10⁹/L, median (IQR)	10.0 (6.9–14.1)	9.6 (6.5–14.4)	9.0 (6.5–14.2)
Platelet count, × 10⁹/L			
Initial value, median (IQR)	250 (175–356)	250 (175–356)	225 (144–312)
Lowest value, median (IQR)	218 (135–316)	170 (115–245)	191 (123–278)
Highest value, median (IQR)	426 (295–591)	451 (327–585)	440 (304–589)
ALT, IU/L			
Always ≤ 40	56 (52.8)	69 (54.8)	125 (53.9)
> 40	50 (47.2)	57 (45.2)	107 (46.1)
ALT when > 40, median (IQR)	81 (55–130)	49 (49–187)	81 (54–136)
AST, IU/L			
Always ≤ 50	58 (54.7)	73 (57.9)	131 (56.5)
> 50	48 (45.3)	53 (42.1)	101 (43.5)
AST when > 50, median (IQR)	80 (58–127)	87 (58–126)	85 (58–126)
Creatinine, μmol/L			
Not measured	2 (1.9)	2 (1.6)	4 (1.7)
Increased for age†††	3 (2.8)	3 (2.4)	6 (2.6)
Peak level for abnormal results, median (IQR)	137 (107–184)	259 (122–345)	161 (122–259)
Required renal replacement therapy	0	0	0
Troponin, ng/L			
Normal, not measured or not recorded‡‡‡	55 (51.9)	111 (88.1)	166 (71.6)
Abnormal§§§	51 (48.1)	15 (11.9)	66 (28.4)
NT-proBNP, pg/mL			
Normal, not measured or not recorded‡‡‡	44 (41.5)	109 (86.5)	153 (65.9)
Peak level of abnormal result, median (IQR)	3215 (1095–9269)	1736 (880–4319)	2685 (1056–6952)

Note: ALT = alanine aminotransferase, AST = aspartate aminotransferase, IQR = interquartile range, MIS-C = multisystem inflammatory syndrome in children, NT-proBNP = N-terminal pro-brain natriuretic peptide.
*Unless indicated otherwise. Patients with confirmed MIS-C had SARS-CoV-2 detected or positive serology.
†Comorbidities among patients with confirmed MIS-C included asthma ($n = 8$, of whom 1 also had Familial Mediterranean Fever, 1 was living with obesity, 1 had idiopathic thrombocytopenic purpura and 1 had sickle cell disease), cancer ($n = 4$, of whom 2 had acute lymphoblastic leukemia and 2 had neuroblastoma), obesity ($n = 2$), autism ($n = 2$), seizure disorder ($n = 2$, of whom 1 had cerebral palsy), congenital heart disease ($n = 1$), Prader–Willi syndrome with hypertension ($n = 1$), chromosomal disorder with prematurity ($n = 1$) and renal tubular acidosis with hypertension and ovalocytosis ($n = 1$).
‡Comorbidities among patients with probable MIS-C included prematurity ($n = 6$), asthma ($n = 6$), periodic fever syndrome ($n = 4$), obesity ($n = 2$), global developmental delay ($n = 3$), sickle cell disease ($n = 1$), liver transplant ($n = 1$), congenital heart disease ($n = 1$), cerebral palsy ($n = 1$), Crohn disease ($n = 1$); 2 others had multiple comorbidities: (i) obesity, congenital heart disease and seizures and (ii) sickle cell disease, global developmental delay and congenital heart disease.
§46 patients missing data on days of fever before admission, 70 patients missing data on total days of fever, 4 patients missing initial leukocyte count, 1 patient missing initial platelet count, 11 patients missing data on ALT.
¶Signs include rash, conjunctivitis, strawberry tongue, red cracked lips or redness or swelling of extremities.
**Gastrointestinal involvement includes vomiting, diarrhea or abdominal pain.
††Cardiac involvement defined as features of myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities (including echocardiographic findings or elevated troponin or NT-proBNP).
‡‡Some children had more than 1 change compatible with MIS-C.
§§Coronary arteries were reported to appear abnormal (dilated, inflamed or edematous), but z scores were not provided or were less than 2.5.
¶¶Abnormal coagulation profile defined as elevated partial thromboplastin time or D-dimers, or international normalized ratio greater than 1.2.
***Thrombosis or evidence of bleeding or disseminated intravascular coagulation; or received erythrocytes, platelets or fresh frozen plasma, tranexamic acid, antifibrinolytics, low-molecular-weight heparin treatment dose or other anticoagulants, such as direct oral anticoagulants.
†††Serum creatinine > 140 μmol/L for children younger than 7 days, 55 μmol/L for children 7–364 days, 100 μmol/L for children aged 1–12 years and 140 μmol/L for those aged 13–17 years (excluding children with chronic renal disease).[14]
‡‡‡Once these parameters were added to the case report form in May 2020, abnormal results were recorded. Abnormal results before this time and and all normal results were not consistently recorded.
§§§We asked only if results were normal or abnormal, without specification of normal values. If result was reported as abnormal, we asked for actual value.

Clinical features

Almost all patients had gastrointestinal involvement (89.2%), mainly abdominal pain, and mucocutaneous findings (84.5%) (Table 1). Children with confirmed MIS-C had a fever for a median total duration of 6 (IQR 4–8) days, compared with 7 (IQR 6–10) days for children with probable MIS-C.

Bacterial coinfections were documented in 12 (5.2%) patients (4 had pharyngitis, 3 had colitis and 5 had urinary tract infections), and 142 (61.2%) received antibiotics, primarily as empiric therapy for sepsis. Viral coinfections were documented in 9 (3.9%) patients (rhinovirus n = 4; rhinovirus and enterovirus n = 3; rhinovirus, enterovirus and parainfluenza n = 1; adenovirus n = 1).

Complications

Cardiac involvement was common (n = 136, 58.6%) including among 76.4% of patients with confirmed MIS-C and 43.6% of those with probable MIS-C (Table 1). Six (2.6%) patients had acute kidney injury; none required renal replacement therapy. Hepatitis affected 120 (51.7%) patients, although none progressed to liver failure.

Most patients (n = 209, 90.1%) had abnormalities in 1 or more coagulation parameters, yet only 3 (1.3%) patients developed clinical hematological manifestations. One patient with confirmed MIS-C had extensive venous thrombosis involving the internal jugular vein, a lower extremity and the lungs. One patient with probable MIS-C developed pulmonary emboli and melena, and another had hematemesis with disseminated intravascular coagulation.

Other complications in patients with confirmed MIS-C included removal of a normal appendix (n = 3, including 1 patient whose appendix was removed 4 days before the hospital admission for MIS-C), anterior uveitis (n = 2), reversible encephalopathy (n = 2) and 1 case each of ileitis requiring total parenteral nutrition, mesenteric adenitis and orchitis. Complications in patients with probable MIS-C included aseptic meningitis (n = 5; none had a virus detected), removal of a normal appendix (n = 2) and 1 case each of ascites, pleural effusion, renal infarction, cholecystitis, orchitis and raised intracranial pressure. One patient with confirmed MIS-C and 3 patients with probable MIS-C

Table 2: Hospital length of stay and level of care for patients admitted to hospital with multisystem inflammatory syndrome in children, according to time of admission

Variable	No. (%)* of patients admitted Mar. 1 to Oct. 31, 2020			No. (%)* of patients admitted Nov. 1, 2020, to Mar. 7, 2021		
	Confirmed n = 28	Probable n = 92	All n = 120	Confirmed n = 78	Probable n = 34	All n = 112
Duration of fever before admission, d, median (IQR)	5 (3–6)	5 (3–6)	5 (3–6)	4 (3–5)	5 (3–6)	4 (3–6)
Total duration of fever, d, median (IQR)	7 (6–9)	6.5 (5–9.5)	7 (5–9)	5.5 (4–8)	6 (6–10)	6 (4–8)
Duration of admission, d, median (IQR)	8 (6.5–10)	5 (3–7)	5 (4–8)	6 (4–8)	7 (4–12)	6 (4–9)
Highest level of care						
Ward admission	18 (64.3)	79 (85.9)	97 (80.8)	39 (50.0)	23 (67.6)	62 (55.4)
No supplemental oxygen	14 (50.0)	76 (82.6)	90 (75.0)	33 (42.3)	20 (58.9)	53 (47.3)
Supplemental oxygen	4 (14.3)	3 (3.3)	7 (5.8)	6 (7.7)	3 (8.8)	9 (8.0)
ICU admission	10 (35.7)	13 (14.1)	23 (19.2)	39 (50.0)	11 (32.4)	50 (44.6)
Observation with or without supplemental oxygen	5 (17.8)	2 (2.2)	7 (5.8)	11 (14.1)	4 (11.8)	15 (13.4)
Vasopressors with or without supplemental oxygen	3 (10.7)	6 (6.5)	9 (7.5)	19 (24.4)	6 (17.6)	25 (22.3)
Noninvasive ventilation and vasopressors	0 (0)	0 (0)	0 (0)	3 (3.8)	1 (2.9)	4 (3.6)
Mechanical ventilation, no vasopressors	0 (0)	1 (1.1)	1 (0.8)	1 (1.3)	0 (0)	1 (0.9)
Mechanical ventilation and vasopressors	2 (7.1)	1 (1.1)	3 (3.3)	4 (5.1)	0 (0)	4 (3.6)
Admission not for MIS-C	0 (0)	3 (3.3)	3 (3.3)	1 (1.3)	0 (0)	1 (0.9)
Treatment†						
Intravenous immunoglobulin	25 (89.3)	69 (75.0)	94 (78.3)	68 (87.2)	32 (94.1)	100 (89.3)
Corticosteroids	12 (42.8)	37 (40.2)	49 (40.8)	57 (73.1)	20 (58.8)	77 (68.8)
Anakinra	0 (0)	3 (3.3)	3 (3.3)	3 (3.8)	4 (11.8)	7 (6.2)
None of the above	2 (7.1)	17 (18.5)	19 (15.8)	4 (5.1)	1 (2.9)	5 (4.5)

Note: ICU = intensive care unit, IQR = interquartile range, MIS-C = multisystem inflammatory syndrome in children.
*Unless indicated otherwise.
†Many patients received a combination of these treatments.

received diagnoses of secondary hemophagocytic lymphohistio-cytosis by the treating clinician.

For treatment, 194 (83.6%) patients received IVIG, 126 (54.3%) patients received corticosteroids and 10 (4.3%) patients received anakinra; 24 (10.3%) patients received none of these treatments (Table 2).

The median length of hospital stay was 6 days, with 69.0% of patients discharged by day 7 and 84.9% discharged by day 10. A ferritin level on admission greater than 500 µg/L was associated with prolonged length of stay (Appendix 2, Supplementary Table 3).

Factors associated with ICU admission

Overall, 73 children (31.5%) required ICU admission, of whom 47 (64.4%) required vasopressors with or without mechanical or noninvasive ventilation. No children required extracorporeal life support or died. Compared with the risk among children aged 0–5 years, the adjusted absolute risk of ICU admission was higher among children aged 6–12 years (43.6% v. 18.4%, adjusted risk difference 25.2%, 95% CI 13.6% to 36.9%) and children aged 13–17 (46.2% v. 18.4%, adjusted risk difference 27.7%, 95% CI 8.3% to 47.2%) (Figure 3 and Table 3). An initial ferritin greater than 500 µg/L was also associated with risk of ICU admission (adjusted risk difference 18.4%, 95% CI 5.6% to 31.3%).

Patients with MIS-C admitted to hospital between Nov. 1, 2020, and Mar. 7, 2021, were more likely to require ICU admission ($n = 50$ of 112, 45%) than those admitted between Mar. 1 and Oct. 31, 2020 ($n = 23$ of 120, 19%, $p < 0.001$) (Table 3), although the difference was not statistically significant after multivariable adjustment (adjusted risk difference 12.3%, 95% CI –0.3% to 25.0%) (Table 3). A stratified analysis of patients with confirmed or probable MIS-C (Appendix 2, Supplementary Table 4; Appendix 5, Supplementary Figure 2, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content) showed a statistically significant increased risk for ICU admission in the later time period (on or after Nov. 1, 2020) among children with probable MIS-C (adjusted risk difference 17.9%, 95% CI 22.7% to 33.6%), in contrast to children with confirmed MIS-C (adjusted risk difference 0.8%, 95% CI –20.4% to 22.0%). For sites in Canada, the risk of ICU admission was higher in the last quarter of the study period (December 2020 to March 2021) than in the first quarter (March to May 2020) (adjusted risk difference 25.3%, 95% CI 6.5% to 44.0%) (Appendix 2, Supplementary Table 5 and Appendix 6, Supplementary Figure 3, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content).

The sensitivity analysis in which we used critical disease as the outcome was consistent with the analysis of ICU admission, with the additional association of mucocutaneous symptoms
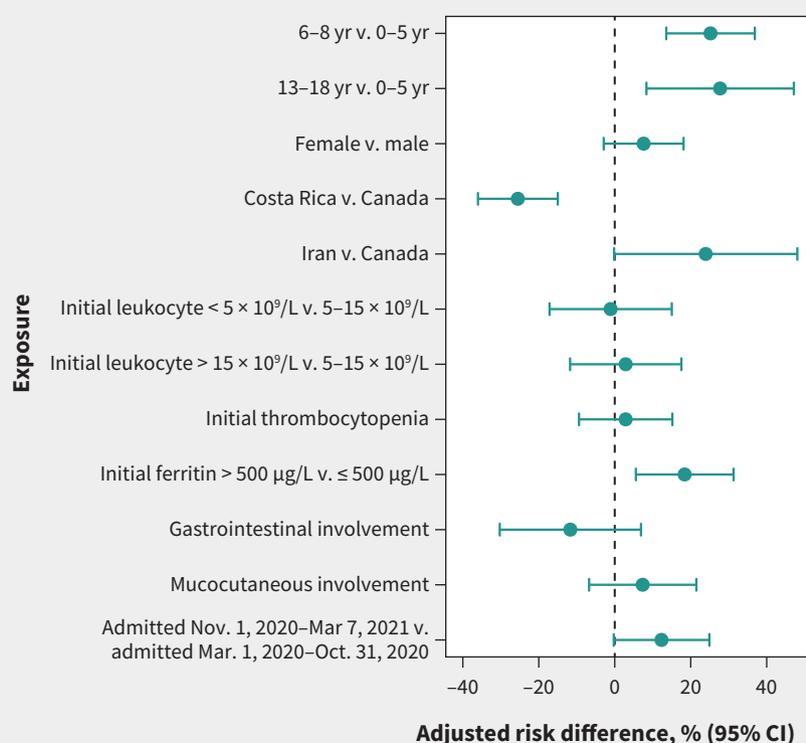
Figure 3: Adjusted risk differences for admission to the intensive care unit. Average marginal effects are presented with adjusted risk differences from multivariable logistic regressions. The reference categories used for adjusted risk differences are the absence of the symptom or the reported category. Models are adjusted for sex, age, country, presence of comorbidity, coinfection, treatment, confirmed case status and admission time. We used 9 different models, each assessing the 9 exposures. Note: CI = confidence interval.

Table 3: Adjusted model estimates of risk factors for intensive care unit admission for patients admitted to hospital with multisystem inflammatory syndrome in children*

Variable	Absolute risk, % (95% CI)	Risk difference, % (95% CI)	Relative risk (95% CI)
Age, yr			
0–5	18.4 (11.6 to 25.2)	–	–
6–12	43.6 (34.4 to 52.8)	25.2 (13.6 to 36.9)	2.37 (1.34 to 3.40)
13–18	46.2 (28.2 to 64.1)	27.7 (8.3 to 47.2)	2.51 (1.14 to 3.88)
Sex			
Male	28.0 (21.3 to 34.8)	–	–
Female	35.6 (27.7 to 43.5)	7.6 (–2.9 to 18.1)	1.27 (0.85 to 1.69)
Country			
Canada	34.7 (28.5 to 40.9)	–	–
Costa Rica	9.2 (1.0 to 17.4)	–25.5 (–36.0 to –15.0)	0.26 (0.03 to 0.51)
Iran	58.7 (28.5 to 40.9)	24.0 (2.3 to 50.9)	1.69 (0.95 to 2.43)
Initial leukocyte count, × 10^9/L†			
< 5	29.2 (14.6 to 43.9)	–1.1 (–17.2 to 15.0)	0.96 (0.44 to 1.49)
5–15	30.3 (24.1 to 36.6)	–	–
> 15	33.2 (20.2 to 46.2)	2.9 (–11.8 to 17.5)	1.10 (0.60 to 1.59)
Initial platelet count, × 10^9/L†			
< 150	33.8 (23.6 to 44.0)	2.9 (–9.4 to 15.2)	1.09 (0.69 to 1.50)
≥ 150	30.9 (24.8 to 37.1)	–	–
Initial ferritin, µg/L†			
≤ 500	26.6 (20.9 to 32.5)	–	–
> 500	45.1 (33.8 to 56.4)	18.4 (5.6 to 31.3)	1.69 (1.12 to 2.26)
Gastrointestinal involvement	30.4 (25.2 to 35.6)	–11.7 (–30.3 to 6.9)	0.72 (0.39 to 1.05)
Mucocutaneous involvement	32.6 (27.0 to 38.1)	7.4 (–6.8 to 21.5)	1.29 (0.59 to 1.99)
Admission period			
Mar. 1–Nov. 1, 2020	24.9 (16.8 to 33.0)	–	–
Nov. 1, 2020–Mar. 7, 2021	37.2 (28.9 to 45.6)	12.3 (–0.3 to 25.0)	1.50 (0.86 to 2.13)

Note: CI = confidence interval.
*Models are adjusted for sex, age, country, presence of comorbidity, coinfection, confirmed case status, treatment and admission time. Average marginal effects are presented with adjusted risk differences from multivariable logistic regressions.
†Number of observations differing from complete data set of 232, leukocytes: 4 missing; platelets: 2 missing; ferritin: 7 missing.

with a higher risk for critical disease (adjusted risk difference 14.0%, 95% CI 4.6% to 23.3%) (Appendix 2, Supplementary Table 6; Appendix 7, Supplementary Figure 4, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content).

Factors associated with cardiac involvement

Among the 232 children, 136 (58.6%) had cardiac involvement, including 90 with changes compatible with MIS-C on echocardiography and 46 with elevated N-terminal pro–brain-type natriuretic peptide or troponin levels, despite normal echocardiography (Table 1). Compared with the risk among children admitted before Nov. 1, 2020, the adjusted absolute risk of cardiac involvement was

significantly higher among children admitted on or after Nov. 1, 2020 (75.0% v. 44.1%; adjusted risk difference 30.9%, 95% CI 17.3% to 44.4%) (Figure 4; Appendix 2, Supplementary Table 7). For Canadian sites, the incidence of cardiac involvement also increased over time (Appendix 8, Supplementary Figure 5, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content). In a stratified analysis of patients with confirmed or probable MIS-C, we observed the association between being admitted on or after Nov. 1, 2020, and increased risk of cardiac involvement among patients with probable MIS-C (Appendix 2, Supplementary Table 8, Appendix 9, Supplementary Figure 6, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.210873/tab-related-content).
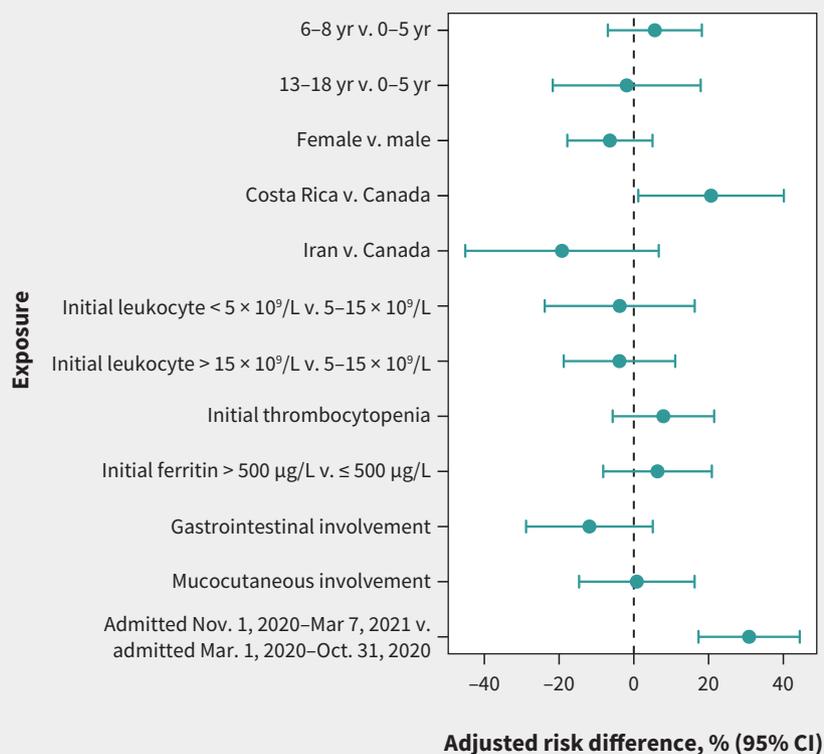
Figure 4: Adjusted risk differences for cardiac involvement. Average marginal effects are presented with adjusted risk differences from multivariable logistic regressions. The reference categories used for risk differences are the absence of the symptom or the reported category. Models are adjusted for sex, age, country, presence of comorbidity, coinfection, confirmed case status and admission time. We used 9 different models, each assessing the 9 exposures. Note: CI = confidence interval.

Interpretation

We found that older age and initial ferritin level were associated with an increased risk of ICU admission among children with MIS-C. Another large study also identified older age as a risk factor (adjusted odds ratio [OR] 2.6 for age 13–20 yr v. 0–5 yr; adjusted OR 1.9 for age 6–12 yr v. 0-5 yr).[9] In the same study, peak inflammatory markers, brain natriuretic peptide, serum troponin and nadir platelet counts were predictive of ICU admission,[9] but initial values are of more practical value than peak and nadir results.

We found evidence for greater severity of MIS-C later in the study period. Exploratory analyses showed that the adjusted risk for cardiac involvement increased in the second period of the study, with a trend toward a higher incidence of ICU admission. However, the severity appeared to be less than in cohorts from the United States observed from March to October 2020[10] and from March 2020 to January 2021.[11] In these studies, 74%[10] and 58% of patients,[11] respectively, required ICU care, compared with 31% in the current study. Mechanical ventilation

was required in 17% in 1 US cohort,[10] compared with 4% in the current study. Similarly, vasopressors were required in 45% in this cohort,[10] compared with 20% in the current study. Differences in case criteria, patient management and threshold for ICU admission may account for some of the variability. We cannot provide a clear explanation for the increased MIS-C severity in the later period of our study. The features of severe MIS-C were widely publicized by May 2020, so it seems unlikely that severe cases were missed early in the study period. SARS-CoV-2 variants of concern have replaced the wild-type virus. It is possible that the immune response to circulating variants alters the severity of COVID-19 and MIS-C when compared with wild-type virus.

Multisystem inflammatory syndrome in children is a new diagnosis, with differing diagnostic criteria that have not been validated. The criteria differ in their requirement for evidence of SARS-CoV-2 infection.[3] In the absence of viral detection or positive serology, CDC criteria require likely exposure to SARS-CoV-2 within the previous 4 weeks. In contrast, WHO criteria do not specify the timing of exposure and do not clarify whether

exposure must be to a specific person or whether exposure includes residence in a community with circulating cases (the definition applied in the current study).[4] Finally, RCPCH criteria[3] and a recent large international study[12] did not require a positive SARS-CoV-2 test or history of exposure and, therefore, all of the 126 children with probable MIS-C in our study would have met these criteria. Most of these children lacked a history of contact with a person with proven SARS-CoV-2 infection. Identifying exposure can be difficult as infected contacts may be asymptomatic or may never have been tested. Confirmation of past infection is complicated as serology is not 100% sensitive[13] and was not available until partway through the study. As more individuals are infected or vaccinated, the diagnostic utility of serology will decline. An international consensus on MIS-C diagnostic criteria is thus necessary to serve both clinical and research purposes and to allow for better comparison of cohorts.

Despite nearly one-third of patients with MIS-C requiring ICU care,[14] recovery was typically rapid, with 85% of patients discharged within 10 days. The role of adjunctive glucocorticoids and the optimal glucocorticoid regimen has not been established, with recent large studies reporting discordant results.[12,15] It is not known whether glucocorticoids could replace IVIG in low-income countries where IVIG is not readily available. Of note, MIS-C resolved without IVIG or glucocorticoids in 10% of patients in our study, mainly among those admitted to hospital early in the study period. It is not clear whether this is because these patients had mild MIS-C or because not all patients require treatment. Long-term follow-up will be important to determine the role of treatment.

Limitations

This study has all the limitations of a chart review. We did not have a formal process to verify the accuracy of data, but generated queries for data that were obviously incorrect (such as when the date of discharge was before the date of admission). We do not have long-term follow-up data, but an MIS-C case series from the US reported resolution of cardiac aneurysms in 45 of 57 patients (79%) and normalization of left ventricular function in 91% of 172 patients 30 days after the initial echocardiogram.[10] In our study, fewer than half of the patients had a positive test for SARS-CoV-2. Diagnostic criteria from MIS-C have not been validated and differ globally. Patients with milder MIS-C may not have been admitted or recognized. Serology for SARS-CoV-2 was not available early in our study period. Race and ethnicity are not reliably recorded in health records in Canada. Although our cohort included data from 15 sites, the total sample size was modest and the use of full models to investigate multiple predictors can lead to small data bias and overfitting. However, our outcomes were common and their number

satisfied the relaxed rule of 10 events per variable when using logistic regression.[16] To assess the more detailed role of comorbidities, a large sample size would be necessary to perform a more elaborate analysis, taking the different and heterogeneous comorbidities into account.

Conclusion

Older age and a high initial level of serum ferritin predict the need for ICU admission among children admitted to hospital with MIS-C. Further research is needed to evaluate long-term outcomes of MIS-C with and without treatment, as well as changes in MIS-C severity and short- and long-term outcomes with emerging variants of concern.

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Affiliations: Department of Epidemiology (Merckx), Biostatistics and Occupational Health, McGill University, Montréal, Que.; Department of Pediatrics (Cooke, Dewan, Restivo), University of Calgary, Calgary, Alta.; Department of Pediatrics (El Tal, Bitnun, Morris, Yeh, Yea, Gill), University of Toronto, Toronto, Ont.; Department of Pediatrics (Papenburg, Lefebvre, Scuccimarri), McGill University, Montréal, Que.; Department of Pediatrics (Ulloa-Gutierrez, Brenes-Chacon, Yock-Corrales, Ivankovich-Escoto, Soriano-Fallas, Hernandez-de Mezerville), Hospital Nacional de Niños Dr. Carlos Sáenz Herrera, Caja Costarricense de Seguro Social, San José, Costa Rica; Department of Pediatrics (Nateghian, Haghighi Aski, Manafi), Iran University of Medical Sciences, Tehran, Iran;

Department of Pediatrics (Dwilow, Bullard), University of Manitoba, Winnipeg, Man.; Department of Pediatrics (Lopez, Sadarangani, Roberts), University of British Columbia; Vaccine Evaluation Center (Sadarangani), BC Children's Hospital Research Institute, Vancouver, BC; Department of Pediatrics (Barton, Petel), Western University, London, Ont.; Department of Pediatrics (Le Saux, Bowes), University of Ottawa, Ottawa, Ont.; Department of Pediatrics (Purewal, Lautermilch, Tehseen), University of Saskatchewan, Saskatoon, Sask.; Department of Pediatrics (Bayliss), Trillium Health Partners, Mississauga, Ont.; Department of Pediatrics (Wong), McMaster University, Hamilton, Ont.; Department of Pediatrics (Leifso), Queen's University, Kingston, Ont.; Department of Pediatrics (Foo), Memorial University, St John's, NL; Department of Pediatrics (Robinson), University of Alberta, Edmonton, Alta.