Differentiating multisystem inflammatory syndrome in children: a single-centre retrospective cohort study

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2021-322290).

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Received 21 April 2021
Accepted 16 June 2021

To cite: Roberts JE, Campbell JI, Gauvreau K, *et al*. *Arch Dis Child* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/archdischild-2021-322290

ABSTRACT

Objective Features of multisystem inflammatory syndrome in children (MIS-C) overlap with other febrile illnesses, hindering prompt and accurate diagnosis. The objectives of this study were to identify clinical and laboratory findings that distinguished MIS-C from febrile illnesses in which MIS-C was considered but ultimately excluded, and to examine the diseases that most often mimicked MIS-C in a tertiary medical centre.

Study design We identified all children hospitalised with fever who were evaluated for MIS-C at our centre and compared clinical signs and symptoms, SARS-CoV-2 status and laboratory studies between those with and without MIS-C. Multivariable logistic LASSO (least absolute shrinkage and selection operator) regression was used to identify the most discriminative presenting features of MIS-C.

Results We identified 50 confirmed MIS-C cases (MIS-C$^+$) and 68 children evaluated for, but ultimately not diagnosed with, MIS-C (MIS-C$^-$). In univariable analysis, conjunctivitis, abdominal pain, fatigue, hypoxaemia, tachypnoea and hypotension at presentation were significantly more common among MIS-C$^+$ patients. MIS-C$^+$ and MIS-C$^-$ patients had similar elevations in C-reactive protein (CRP), but were differentiated by thrombocytopenia, lymphopenia, and elevated ferritin, neutrophil/lymphocyte ratio, BNP and troponin. In multivariable analysis, predictors of MIS-C included age, neutrophil/lymphocyte ratio, platelets, conjunctivitis, oral mucosa changes, abdominal pain and hypotension.

Conclusions Among hospitalised children undergoing evaluation for MIS-C, children with MIS-C were older, more likely to present with conjunctivitis, oral mucosa changes, abdominal pain and hypotension, and had higher neutrophil/lymphocyte ratios and lower platelet counts. These data may be helpful for discrimination of MIS-C from other febrile illnesses, including bacterial lymphadenitis and acute viral infection, with overlapping features.

What is already known on this topic?

- Laboratory features of multisystem inflammatory syndrome in children (MIS-C) include lymphopenia, thrombocytopenia, and elevated C-reactive protein (CRP), procalcitonin, troponin and B-type natriuretic peptide.
- Clinical features include abdominal pain, shock and physical exam findings of Kawasaki disease.

What this study adds?

- The most discriminative features of MIS-C were older age, conjunctivitis, oral mucosa changes, abdominal pain and hypotension, higher neutrophil/lymphocyte ratios and lower platelet counts.
- CRP did not differentiate between MIS-C and alternative diagnoses among hospitalised children with fever.
- MIS-C may be confused with other infectious, inflammatory and oncologic causes of fever. The most common alternative diagnoses in our cohort were viral infection, bacterial lymphadenitis and urinary tract infection.

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 is characterised by fever, systemic inflammation and organ dysfunction. Identifying unique features of MIS-C is critical for timely recognition and treatment, but presents a challenge for clinicians, as MIS-C case definitions overlap with other common conditions.[1–3] Studies comparing MIS-C with other hyperinflammatory syndromes including Kawasaki disease (KD) showed overlapping laboratory parameters and most included critically ill MIS-C patients, limiting generalisability to children with more mild manifestations.[4–6] Recent comparisons of MIS-C to other febrile illnesses in outpatient and emergency department settings showed higher C-reactive protein (CRP) and procalcitonin in MIS-C, but this may be related to differences in acuity.[7 8] Thus, for clinicians attempting to discriminate between MIS-C and other febrile illness in children with similar clinical presentations, the existing literature offers limited guidance.

We aimed to identify epidemiologic, physical examination and laboratory findings that distinguished MIS-C from other febrile illnesses, and to describe alternative diagnoses that mimicked MIS-C.

METHODS

Our patient population included hospitalised children for whom a diagnosis of MIS-C was considered after initial triage at our single, free-standing paediatric hospital in Boston, Massachusetts. Per our hospital's MIS-C evaluation protocol,

rheumatology was consulted for patients in whom the emergency department or inpatient team had concern for MIS-C. The protocol suggests considering MIS-C in children with clinical features consistent with the Centers for Disease Control (CDC) definition[1] and CRP ≥3 mg/dL, the latter stemming from definitions of systemic inflammation in incomplete KD.[9] Rheumatologists triaged patients and recommended echocardiogram in children for whom there was sufficiently high suspicion for MIS-C. Children evaluated with rheumatology consultation and echocardiogram were included in our study. We included confirmed MIS-C patients (MIS-C$^+$) admitted between April 2020 and January 2021, during which time our hospital experienced two peaks of MIS-C. Children who were evaluated for MIS-C but ultimately received alternative diagnoses (MIS-C$^-$) were admitted between May and August 2020, as complete data were only available for the first surge.

The primary outcome was diagnosis of MIS-C. Rheumatologists and cardiologists adjudicated MIS-C diagnoses using the CDC definition.[1] Patients treated for acute COVID-19 without clinical suspicion for MIS-C were excluded. This study was determined exempt by the Boston Children's Hospital IRB (#P00035838).

Predictors included demographics, exam findings and symptoms, and laboratory values at time of presentation. First laboratory values were used for analysis; while most were drawn within 12 hours of presentation, we accepted values after 12 hours if no earlier testing had been obtained. For patients transferred to our hospital, initial laboratory data were obtained from scanned records. We gathered data on non-SARS-CoV-2 infections, hospital course and outcomes including coronary artery dilation (z-score 2–2.5) or aneurysm (z-score ≥2.5) and left ventricular dysfunction (ejection fraction <55%). KD clinical symptoms were defined per published criteria.[9]

For patients residing in Massachusetts, we obtained city-level, or if Boston residents, neighborhood-level, COVID-19 case numbers and population through the end of January 2021 and calculated area-level COVID-19 incidence for each patient's residence.[10 11]

We compared laboratory values, SARS-CoV-2 testing and exposure, and clinical signs and symptoms of MIS-C$^+$ and MIS-C$^-$ patients using the Wilcoxon rank sum and Fisher's exact tests. Multivariable logistic regression using adaptive LASSO (least absolute shrinkage and selection operator) for variable selection was used to identify features best able to discriminate MIS-C. Because positive SARS-CoV-2 testing is part of the case definition of MIS-C, this was not considered for inclusion in the multivariable model. Haemoglobin was correlated with age and therefore not considered for inclusion in the model; troponin was not included due to a high proportion of missing data and non-random pattern of missing values.

RESULTS

Patient population and SARS-CoV-2 exposure

We identified 50 patients with confirmed MIS-C (MIS-C$^+$) and 68 children evaluated for, but ultimately not diagnosed with, MIS-C (MIS-C$^-$). Children with MIS-C were more likely to be male and older (table 1). We identified no statistically significant differences in race or ethnicity, although the proportion of black children was higher in the MIS-C$^+$ group, and statistical comparisons were limited by high proportions of missing data.

Children diagnosed with MIS-C were more likely to have positive SARS-CoV-2 PCR testing at presentation, positive SARS-CoV-2 serology, known contact with a SARS-CoV-2-positive individual and personal history of known COVID-19 infection (tables 1 and 2). There was a trend towards living in areas with higher COVID-19 rates in MIS-C$^+$ compared to MIS-C$^-$, but this did not reach statistical significance.

Table 1 Demographics and COVID exposures

	MIS-C$^+$ (n=50)	MIS-C$^-$ (n=68)	
	Median (IQR) or n (%)	Median (IQR) or n (%)	P value
Age (years)	9.65 (6.22–14.0)	3.15 (1.28–7.88)	<0.001
Male	33 (66)	30 (44)	0.025
Race/Ethnicity			
White	15 (30)	30 (44)	0.23
Black	9 (18)	8 (12)	
Other*	12 (24)	19 (28)	
Missing/declined to answer	14 (28)	11 (16)	
Hispanic/Latino	11 (22)	12 (18)	0.64
City/Neighbourhood COVID incidence (n=94)†	0.0824 (0.059–0.109)	0.0647 (0.049–0.097)	0.059
Known history of COVID infection	20 (40)	4 (6)	<0.001
Known contact with COVID positive individual	31 (62)	10 (15)	<0.001

*Two patients selected two races and are included in this category.
†Reported only for Massachusetts residents. Incidence reported as cases per population.
MIS-C, multisystem inflammatory syndrome in children.

Alternative diagnoses

Of 68 MIS-C$^-$ patients, 23 were diagnosed with bacterial infections, 10 with acute viral infections, 12 with autoimmune/

Table 2 Laboratory values and SARS-CoV-2 testing at presentation

	MIS-C$^+$ (n=50)	MIS-C$^-$ (n=68)	
Laboratory values	Median (IQR) or n (%)	Median (IQR) or n (%)	P value
CRP (mg/dL)	11.1 (5.6–20.5)	9.14 (5.1–13.6)	0.13
ESR (n=117)	42 (22–55)	54 (26.5–76.5)	0.045
D-dimer (mcg/mL FEU) (n=117)	2.08 (1.19–3.16)	1.26 (0.79–2.26)	0.017
White blood cell count (K cells/µL)	9.26 (6.77–13.0)	14.7 (10.5–19.0)	<0.001
Absolute neutrophil count (K cells/µL)	6.88 (4.77–9.09)	9.59 (5.75–13.2)	0.02
Absolute lymphocyte count (K cells/µL)	1.27 (0.81–2.06)	2.58 (1.23–4.61)	<0.001
Neutrophil/Lymphocyte ratio	5.20 (3.12–9.98)	3.42 (1.61–5.97)	0.006
Haemoglobin (g/L)	120 (111–134)	111 (102–121)	0.001
Platelets (K cells/µL)	192 (141–238)	302 (218–384)	<0.001
Ferritin (ng/mL) (n=116)	366 (210–921)	146 (106–220)	<0.001
Ferritin/CRP ratio (n=116)	38 (24–76)	19 (12–43)	<0.001
Procalcitonin (pg/mL) (n=105)	1.19 (0.40–3.86)	0.72 (0.23–2.2)	0.043
AST (u/L)	39 (27.8–57)	35 (25.5–53.3)	0.48
ALT (u/L)	29 (17–61)	16 (13–23)	<0.001
Albumin (g/dL) (n=116)	3.5 (3.1–4)	3.9 (3.6–4.1)	0.003
BNP (pg/mL) (n=111)	75 (20.5–367)	15.5 (10–57.8)	<0.001
Troponin—abnormal* (n=107)	9 (19%)	1 (2%)	0.005
SARS-CoV-2 PCR positive (n=115)	14 (29%)	2 (3%)	<0.001
SARS-CoV-2 antibody positive (n=111)	40 (87%)	7 (11%)	<0.001

*Not performed in 7, not reportable in 4.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MIS-C, multisystem inflammatory syndrome in children.

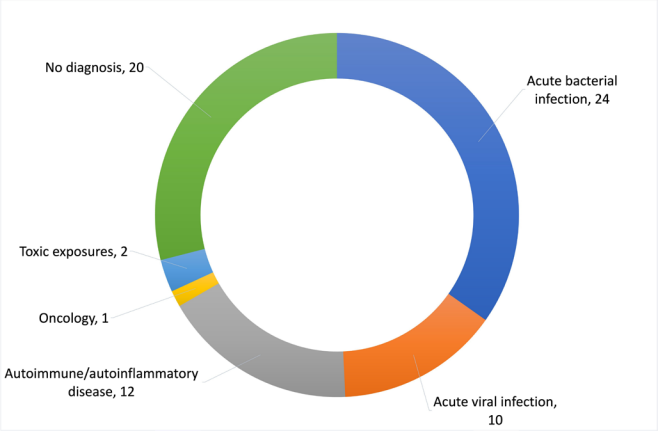

Figure 1 Summary of non-MIS-C diagnoses. MIS-C, multisystem inflammatory syndrome in children.

autoinflammatory disorders, 2 with e-cigarette or vaping product use-associated lung injury (EVALI) and 1 with Langerhans cell histiocytosis (figure 1; table 3). The most common alternative diagnoses were bacterial lymphadenitis (7), urinary tract infection (4), KD (4) and acute EBV infection (3). All patients diagnosed with bacterial lymphadenitis had supportive imaging and/or improvement with antibiotics to support a bacterial aetiology, and four out of seven had isolation of bacterial species commonly implicated in bacterial lymphadenitis (*Staphylococcus* or *Streptococcus*). All children with urinary tract infection had positive urine cultures. No diagnosis was determined for 20, although acute viral syndromes were suspected for many.

Clinical signs and symptoms

Conjunctivitis, abdominal pain, fatigue and oral mucosa changes at presentation were significantly more common among MIS-C$^+$ patients (table 4). Rash was observed in half of both MIS-C$^+$ and MIS-C$^-$ patients. Frequency of extremity changes, lymphadenopathy, cough, shortness of breath, vomiting, diarrhoea, headache and altered mental status were not different between both groups. MIS-C$^+$ patients also reported chest pain, neck pain, dizziness, syncope and myalgias. Duration of fever prior to presentation was similar, with a median of 5 days of fever in MIS-C$^+$ and MIS-C$^-$ patients. Median total duration of fever was 6 days in both groups (IQR 5–7 days in MIS-C$^+$; 4.75–9 days in MIS-C$^-$).

Both MIS-C$^+$ and MIS-C$^-$ patients had a median of one clinical criteria of KD (rash, conjunctivitis, oral mucosa changes, hand/foot changes, lymphadenopathy ≥1.5 cm), although MIS-C$^-$ patients were more likely to have fewer than two criteria than MIS-C$^+$ patients (75% vs 54%, p=0.019) and only two MIS-C$^+$ patients (4%) fulfilled complete KD criteria, compared with 1 (1%) in the MIS-C$^-$ group (online supplemental table 1). The most common KD criteria in MIS-C$^+$ patients were conjunctivitis (58%) and rash (46%). Teenage MIS-C$^+$ patients had fewer KD symptoms, with 31% having rash or conjunctivitis, one patient (6%) having lymphadenopathy ≥1.5 cm, and none having extremity or oral mucosa changes; 81% had fewer than two KD criteria (online supplemental table 1). Lymphadenopathy ≥1.5 cm was found in only one MIS-C$^+$ child; of four children with lymphadenopathy without other KD features, none were diagnosed with MIS-C.

MIS-C$^+$ patients were more likely to have hypoxaemia, tachypnoea and hypotension. In further analyses of hypotension, we evaluated initial blood pressure in all patients and found that only 5 (10%) of MIS-C$^+$ patients had systolic hypotension on their first recorded vital signs, compared with the 19 (39%) who had hypotension at some point during the initial 24-hour observation period.

Table 3 Detailed summary of alternate diagnoses among MIS-C$^-$ patients

Diagnosis	Number
Bacterial infection	24
Anaplasmosis	1
Bacterial lymphadenitis	7
Dental abscess	1
Labial abscess	1
Lyme disease	2*
Mycobacterium flavescens mediastinal lymphadenitis	1
Non-typhoidal *Salmonella enteritis*	2
Pneumonia (presumed bacterial)	1
Retropharyngeal abscess	1
Ruptured AOM/parotid abscess/infected branchial cleft cyst	1
Urinary tract infection	4
Small bowel intussusception/necrosis and peritonitis	1
Staphylococcal toxic shock syndrome	1
Acute viral infection	10
Acute CMV	1
Acute EBV	3*
Adenovirus URI	2
Coxsackievirus-associate herpangina	1
Human metapneumovirus URI	2
Rhinovirus URI	1
Autoimmune/autoinflammatory disease	12
Autoimmune cholangiopathy	1
Coeliac disease	1
Inflammatory bowel disease	1
Kawasaki disease	4
Kikuchi disease (complicated by MAS/HLH)	1
Systemic JIA (complicated by MAS/HLH)	1
PFAPA	2
Urticaria multiforme	1
Oncology	1
Langerhans cell histiocytosis	1
Toxic exposures	2
EVALI	2
No diagnosis	20
Total patients	68*

*One patient was diagnosed with both Lyme and EBV infection.
AOM, acute otitis media; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EVALI, e-cigarette or vaping product use-associated lung injury; HLH, hemophagocytic lymphohistiocytosis; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MIS-C, multisystem inflammatory syndrome in children; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; URI, upper respiratory infection.

Laboratory features

The MIS-C$^+$ and MIS-C$^-$ groups had similar CRP (table 2). MIS-C$^+$ patients had significantly higher ferritin, procalcitonin, BNP and troponin, and lower platelets, white blood cells and lymphocytes. Neutrophil/lymphocyte and ferritin/CRP ratios were higher in MIS-C$^+$. MIS-C$^+$ patients more frequently had abnormal troponin.

Multivariable regression

In the multivariable LASSO model, the most discriminative predictors of MIS-C diagnosis were older age, higher neutrophil/

Table 4 Clinical signs and symptoms at presentation

	MIS-C$^+$ (n=50)	MIS-C$^-$ (n=68)	
	n (%)	n (%)	P value
Kawasaki disease criteria			
Rash	23 (46)	31 (46)	1
Oral mucosa changes	12 (24)	5 (7)	0.016
Conjunctivitis	29 (58)	10 (15)	<0.001
Hand/Foot redness or swelling	5 (10)	9 (13)	0.77
Lymphadenopathy ≥1.5 cm	1 (2)	7 (10)	0.14
Symptoms			
Abdominal pain	29 (58)	10 (15)	<0.001
Vomiting	21 (42)	21 (31)	0.25
Diarrhoea	20 (40)	21 (31)	0.33
Cough	9 (18)	5 (7)	0.09
Shortness of breath	2 (4)	2 (3)	1
Fatigue	14 (28)	7 (10)	0.016
Headache	14 (28)	9 (13)	0.06
Altered mental status	1 (2)	4 (6)	0.39
Days of fever at presentation—*median (IQR)*	5 (3–6)	5 (3–7)	0.74
Vital signs within 24 hours of presentation			
Fever	36 (72)	53 (78)	0.52
Tachycardia	41 (82)	53 (78)	0.65
Tachypnoea	37 (74)	24 (35)	<0.001
Hypotension (n=117)*	19 (39)	4 (6)	<0.001
Hypoxaemia (O_2<95%)	13 (26)	5 (7)	0.008

*Not available for patient requiring extracorporeal membrane oxygenation.
MIS-C, multisystem inflammatory syndrome in children.

lymphocyte ratio, lower platelets and presence of conjunctivitis, oral mucosa changes, abdominal pain and hypotension.

Hospital course and cardiac outcomes

Median hospital length of stay was 5.1 days (IQR 3.1–7.5) in MIS-C$^+$ patients versus 2.8 days (1.9–5.9) in MIS-C$^-$ patients (p=0.001). Half of MIS-C$^+$ patients required admission to an intensive or intermediate acute care unit, compared with 16% of MIS-C$^-$ patients (p<0.001), and MIS-C$^+$ patients were more likely to require vasopressors (28% vs 7%, p=0.004). More MIS-C$^+$ children required respiratory support (30% vs 7%, p=0.002), primarily low flow nasal cannula or non-invasive positive pressure ventilation. Two MIS-C$^+$ patients and one MIS-C$^-$ patient required mechanical ventilation. One child in the MIS-C$^+$ group required extracorporeal membrane oxygenation. There were no in-hospital deaths.

Coronary artery dilation was found in 4% of MIS-C$^+$ patients, coronary artery aneurysm in 12% of MIS-C$^+$ patients, and left ventricular dysfunction was present in 48% of MIS-C$^+$ patients. The majority (71%) of MIS-C$^+$ patients requiring vasopressors had ventricular dysfunction, while 29% had normal ventricular function on all echocardiograms.

In the MIS-C$^-$ group, one patient (1%) had coronary dilation, one (1%) had aneurysm and one (1%) had ventricular dysfunction. One patient had mild coronary dilation in the setting of anaplasmosis; coronary dimensions normalised after resolution of fever. The other MIS-C$^-$ child with aneurysm was treated for bacterial lymphadenitis and did not meet criteria for MIS-C (no SARS-CoV-2 exposure and negative serologies) or KD but was followed by cardiology for presumed incidental finding of coronary aneurysm. The MIS-C$^-$ child with ventricular dysfunction had borderline ejection fraction (52%) in the setting of tachycardia and improved with antibiotic treatment for bacterial lymphadenitis.

DISCUSSION

We identified clinical findings and laboratory values in children with MIS-C that differed from those with alternative diagnosis. The most distinguishing features favouring MIS-C were older age, higher neutrophil/lymphocyte ratio, lower platelets, and presence of conjunctivitis, oral mucosa changes, abdominal pain and hypotension.

Alternative diagnoses

We identified a variety of infectious and inflammatory diagnoses in patients evaluated for MIS-C. We and others have previously noted that non-SARS-CoV-2 infections can mimic findings of MIS-C.[12–14] Many children had confirmed or suspected viral infections, including acute EBV. Bacterial infections, notably bacterial lymphadenitis and urinary tract infections, were common in the MIS-C$^-$ cohort; Lyme disease or anaplasmosis were identified in three patients and should be considered in endemic areas. Inflammatory diseases including KD, PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis), and Kikuchi syndrome and systemic juvenile idiopathic arthritis leading to macrophage activation syndrome were also identified. The most frequent symptoms in the MIS-C$^+$ group included fever, abdominal pain and rash, which are non-specific and can be found in other febrile illnesses.

Clinical features and demographics

Early reports described MIS-C as a variant of KD, and clinical features of KD are included in evaluation guidelines.[15–18] However, subsequent series have reported varied incidence of KD features and differences in laboratory parameters and demographics between these diseases.[4–6 19–21] The majority of MIS-C$^+$ patients in our cohort had few or no clinical features of KD. This was particularly pronounced in older patients, who had higher rates of cardiac involvement despite fewer KD features, as reported previously.[20] Our data are consistent with reports that KD features do not identify most children with MIS-C and do not predict risk for coronary artery aneurysm development.[5 19 22] Furthermore, some features of KD such as unilateral lymphadenopathy are uncommon in MIS-C and should prompt consideration of bacterial lymphadenitis, which was a frequent alternative diagnosis in MIS-C$^-$.

Although MIS-C$^-$ patients had various infectious and non-infectious abdominal processes, presence of abdominal pain was highly associated with MIS-C, suggesting that abdominal pain in the presence of recent SARS-CoV-2 infection or exposure should trigger consideration of MIS-C.

We identified hypotension within the first 12 hours as a predictor of MIS-C diagnosis, although few children presented with hypotension on their first vital signs. Children with MIS-C may not present in overt shock, and development of haemodynamic instability during observation may be an important clinical sign. Importantly, nearly one-third of MIS-C$^+$ patients requiring vasopressors did not having any evidence of ventricular dysfunction, suggesting that shock may be distributive, and clinicians must maintain high suspicion for haemodynamic instability even in the presence of normal ventricular function on echocardiogram.

We did not find a difference in race or ethnicity between MIS-C$^+$ and MIS-C$^-$; however, numerically more black children were in the MIS-C$^+$ group, and missing data and small numbers of

black and Hispanic children may have resulted in this analysis being underpowered to detect differences. Similarly, although we did not find a statistically significant difference, there was a trend towards higher city and neighbourhood COVID-19 incidence in areas where MIS-C$^+$ children resided; the size of our cohort may have limited detecting an association. The lack of widely available SAR-CoV-2 testing early in the pandemic may have impacted these results by underestimating rates of infection in neighbourhoods where community spread was occurring undetected. Our previous work demonstrated that MIS-C$^+$ children were more likely to reside in neighbourhoods with lower socioeconomic status.[23] Knowledge of local SARS-CoV-2 incidence and assessment of social risk factors that have been identified as predictors of paediatric COVID-19 infection, such as overcrowding, parental occupation and public transportation use, remain important tools for clinicians in evaluating children for MIS-C.[24]

Laboratory findings distinguishing MIS-C$^+$

Our findings of elevated neutrophil/lymphocyte ratio and thrombocytopenia as discriminating features of MIS-C have been reported previously in MIS-C and in patients with severe acute COVID-19.[4–6 15 16 19 20 25] While platelet count was a discriminative feature, the mean MIS-C$^+$ platelet count was only mildly low. Mild thrombocytopenia in the presence of systemic inflammation, which is often accompanied by elevated platelets, should prompt consideration of MIS-C in appropriate clinical contexts. In contrast to earlier comparisons, CRP was similar between MIS-C$^+$ and MIS-C$^-$ in our cohort.[7 8 25] This may be because elevated CRP is a non-specific marker of inflammation and was more elevated in our comparison group of hospitalised children than in other cohorts that used outpatients as controls. In contrast, ferritin and ferritin/CRP ratio were higher in patients with MIS-C, suggesting that that among inflamed patients, ferritin may be a more relevant marker to differentiate patients with MIS-C. Procalcitonin is frequently used as a marker of bacterial infection and may be elevated in severe viral infection,[26 27] but is also reported in MIS-C.[8 28 29] We found significantly higher procalcitonin in MIS-C$^+$ than MIS-C$^-$, although observed ranges overlapped.

Limitations

This study had several limitations, including that MIS-C evaluation reflects our hospital's practices, with frequent involvement of rheumatology and cardiology. We included only hospitalised children per the CDC definition,[1] and our hospital's algorithm suggested considering MIS-C when CRP ≥3 mg/dL, which may have limited identification of mild cases. The identification of and need for treatment in children with post-COVID inflammatory symptoms who do not require hospitalisation or have only mildly elevated inflammatory markers remain important areas of investigation. Our study reflects local prevalence of alternative diagnoses; thus, findings may not be generalisable to other regions. Changing prevalence of SARS-CoV-2 may impact the utility of testing and exposure history for discriminating MIS-C. Finally, MIS-C is an emerging clinical syndrome without a gold standard diagnosis, and the finding that features included in MIS-C case definitions are more common in MIS-C$^+$ may be expected. Importantly, however, we show that only some of the features in case definitions effectively discriminate between MIS-C and alternative diagnoses.

Conclusions

We identified features that predicted diagnosis of MIS-C among hospitalised children with fever. The most discriminative features were older age, higher neutrophil/lymphocyte ratio, lower platelets, and presence of conjunctivitis, oral mucosa changes, abdominal pain and hypotension. These data can assist in distinguishing MIS-C from alternative diagnoses and may improve diagnostic algorithms currently based on expert opinion.

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Contributors JER: Contributed to study conceptualisation and design, collected data, performed analysis, and drafted the initial manuscript, and reviewed and revised the manuscript. JIC: Contributed to study design, data collection, interpretation, and visualisation, and reviewed and revised the manuscript. KG: Oversaw design of statistical analysis plan, performed multivariable analysis, and reviewed and revised the manuscript. GSL: Contributed to data interpretation and reviewed and revised the manuscript. MBS and JN: Contributed to study conceptualisation and design, and reviewed and revised the manuscript. AD: Conceptualised and designed the study, supervised data collection, analysis, and interpretation, and reviewed and revised the manuscript.

Funding Dr Roberts was supported by NIH grant 5T32AI007512-34. Dr Campbell was supported by AHRQ grant number T32HS000063. Drs Dionne and Newburger were supported by The McCance Foundation. Dr Son was supported by the Samara Jan Turkel Center.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Deidentified data may be made available on reasonable request to the corresponding author. All data access will be subject to a data use agreement and approval by the Boston Children's Hospital Institutional Review Board.

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