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Clinical Research

Kawasaki Disease in the Time of COVID-19 and MIS-C: The International Kawasaki Disease Registry

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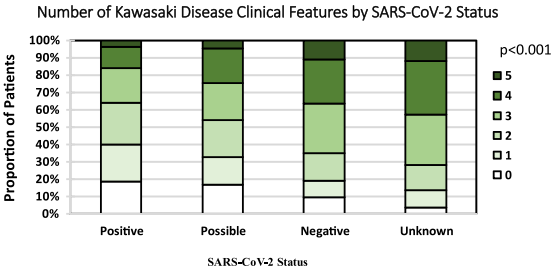
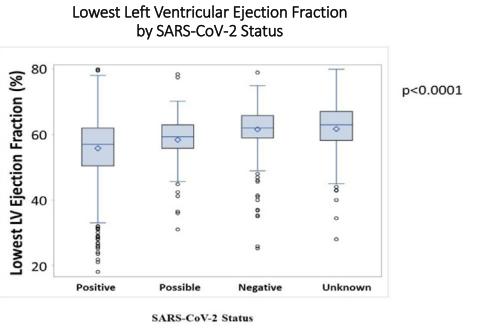
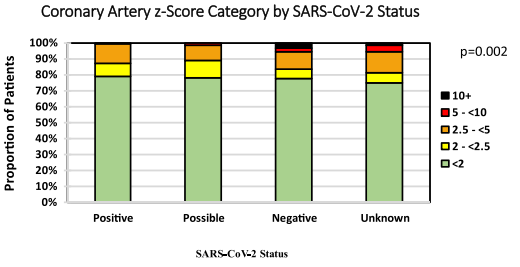
See editorial by Batu, pages 73–76 of this issue.

Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) and Kawasaki disease (KD) share common clinical features and outcomes; evidence of prior SARS-CoV-2 infection is a key differentiating feature for MIS-C and KD. The International KD Registry (IKDR) enrolled 2345 contemporaneous MIS-C and KD patients. Patients were then grouped by degree of evidence of prior infection and compared.







Patients with evidence of prior SARS-CoV-2 infection have clinical features and outcomes more suggestive of MIS-C. With a rising prevalence of prior infection in the population and the impact of vaccination, this evidence may prove increasingly elusive.

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ABSTRACT

Background: Patients with multisystem inflammatory syndrome in children (MIS-C) and Kawasaki disease (KD) have overlapping clinical features. We compared demographics, clinical presentation, management, and outcomes of patients according to evidence of previous SARS-CoV-2 infection.

Methods: The International Kawasaki Disease Registry (IKDR) enrolled KD and MIS-C patients from sites in North, Central, and South America, Europe, Asia, and the Middle East. Evidence of previous infection was defined as: Positive (household contact or positive polymerase chain reaction [PCR]/serology), Possible (suggestive clinical features of MIS-C and/or KD with negative PCR or serology but not both), Negative (negative PCR and serology and no known exposure), and Unknown (incomplete testing and no known exposure).

Results: Of 2345 enrolled patients SARS-CoV-2 status was Positive for 1541 (66%) patients, Possible for 89 (4%), Negative for 404 (17%) and Unknown for 311 (13%). Clinical outcomes varied significantly among the groups, with more patients in the Positive/Possible groups presenting with shock, having admission to intensive care, receiving inotropic support, and having longer hospital stays. Regarding cardiac abnormalities, patients in the Positive/Possible groups had a higher prevalence of left ventricular dysfunction, and patients in the Negative and Unknown groups had more severe coronary artery abnormalities.

Conclusions: There appears to be a spectrum of clinical features from MIS-C to KD with a great deal of heterogeneity, and one primary differentiating factor is evidence for previous acute SARS-CoV-2 infection/exposure. SARS-CoV-2 Positive/Possible patients had more severe presentations and required more intensive management, with a greater likelihood of ventricular dysfunction but less severe coronary artery adverse outcomes, in keeping with MIS-C.

RÉSUMÉ

Introduction : Le syndrome inflammatoire multisystémique de l'enfant (SIME) et la maladie de Kawasaki (MK) ont des caractéristiques cliniques qui se chevauchent. Nous avons comparé les données démographiques, le tableau clinique, la prise en charge et les résultats cliniques des patients en fonction des preuves d'une infection antérieure au SRAS-CoV-2.

Méthodes : Des patients atteints de la MK et du SIME d'établissements de l'Amérique du Nord, de l'Amérique centrale, de l'Amérique du Sud, de l'Europe, de l'Asie et du Moyen-Orient étaient inscrits au registre international de la maladie de Kawasaki (IKDR, de l'anglais *International Kawasaki Disease Registry*). Les preuves d'une infection antérieure étaient définies comme suit : positives (contacts familiaux ou réaction en chaîne par polymérase [PCR, de l'anglais *polymerase chain reaction*])/sérologie positives), possibles (caractéristiques cliniques suggestives de SIME et/ou de la MK, une PCR ou une sérologie négative, mais non les 2), négatives (PCR et sérologie négatives, et aucune exposition connue) et inconnues (tests incomplets et aucune exposition connue).

Résultats : Au sein des 2 345 patients inscrits, 1 541 (66 %) patients étaient positifs au SRAS-CoV-2 (groupe positif), 89 (4 %) étaient possiblement positifs ou non (groupe possible), 404 (17 %) étaient négatifs (groupe négatif), et 311 (13 %) l'ignoraient (groupe inconnu). Les résultats cliniques variaient de façon significative entre les groupes : les patients des groupes positif et possible avaient plus souvent un choc, étaient plus souvent admis aux soins intensifs, recevaient plus souvent un traitement inotrope et avaient plus souvent des séjours à l'hôpital plus longs. En ce qui concerne les anomalies cardiaques, la prévalence de dysfonction ventriculaire gauche chez les patients des groupes positif et possible était plus élevée, et les patients des groupes négatif et inconnu avaient plus souvent des anomalies plus graves des artères coronaires.

Conclusions : Il semble y avoir un spectre de caractéristiques cliniques d'une grande hétérogénéité entre le SIME et la MK, et l'un des principaux facteurs de différenciation est la preuve d'une infection/exposition aiguë précédente au SRAS-CoV-2. Les patients qui étaient positifs/possiblement positifs ou non au SRAS-CoV-2 avaient des symptômes plus graves et avaient plus souvent besoin d'une prise en charge aux soins intensifs, et une plus forte probabilité de dysfonction ventriculaire, mais moins d'anomalies défavorables aux artères coronaires en relation avec le SIME.

Kawasaki disease (KD), first described in 1967, is characterised by systemic inflammation that may lead to coronary artery aneurysms (CAAs), myocardial ischemia, and death.[1] Despite more than 50 years of research, the cause remains unknown.[2] When a new illness, multisystem inflammatory syndrome in children (MIS-C) was identified during the 2019 novel coronavirus disease (COVID-19) pandemic and had clinical similarities to KD, experts around the globe hoped that its emergence would facilitate the identification of an underlying etiology for KD.[3-7] Similarly to KD, MIS-C is characterised by systemic inflammation[2] and can be associated with cardiac complications.[8,9] The overlap in the case definition and clinical features between MIS-C and KD suggests there is a possibility of at least partially overlapping immunopathogenesis.[10,11] The diagnostic criteria for MIS-C remain broad, relying on the presence of nonspecific clinical and laboratory findings that are in common with other paediatric inflammatory conditions, particularly KD.[12-15] Many patients with MIS-C meet the case definition for complete or atypical KD, and vice versa. In those with clinical overlap, one key distinguishing diagnostic feature is previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or exposure in the case definition for MIS-C, although outbreaks

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See page 69 for disclosure information.

of KD have been possibly associated with other types of coronavirus infection in the past.[10,16,17] However, several unique challenges have continued to present diagnostic dilemmas between the two. Early in the COVID-19 pandemic, diagnostic testing for SARS-CoV-2 was not widely available. More recently, the difficulty has arisen again, as prior infection and vaccination may confound the utility of diagnostic testing. We sought to compare demographics, clinical presentation, management, and outcomes of patients according to degree of evidence of prior SARS-COV-2 infection. We hypothesised that the level of confidence in SARS-COV-2 infection or exposure status, from confirmed positive to confirmed negative, would manifest in a spectrum of clinical characteristics spanning from MIS-C to KD.

Methods

International Kawasaki Disease Registry

The International Kawasaki Disease Registry (IKDR) was established in 2013 with members from the United States and Canada to determine outcomes of CAAs after KD.[18-20] The emergence of MIS-C in March 2020 and its clinical overlap with KD prompted the IKDR to expand data collection to Central and South America, Europe, Asia, and the Middle East. The scope was also increased from only patients with KD and CAAs to prospectively enroll patients diagnosed with 1) acute, confirmed, or suspected diagnosis of complete or incomplete KD, or KD shock syndrome with or without CAAs, and 2) confirmed or suspected MIS-C.

The IKDR protocols were approved by participating centres with informed consent or waiver of consent depending on the jurisdiction. Depending on jurisdiction and when required, the authors confirm that patient consent forms were obtained for this article. After obtaining legal authorisation including data use agreement, each site submitted deidentified data of their patients to the data coordinating centre (DCC) in Toronto, Ontario. Using the Research Electronic Data Capture (REDCap) tool, each site submitted data including demographics, dates of illnesses, clinical presentation, treatment received, and clinical outcomes.[21] Deidentified reports of imaging, including electrocardiography, echocardiography, and cardiac MRI, and serial laboratory findings were submitted directly to the DCC for centralised data entry into REDCap. Data quality was ensured by sending verification queries from the DCC to each participating centre. Only patients with resolved data queries were included in the analyses. Author B.W.M. had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Study design and patient selection

Patients with a site diagnosis of either acute KD or MIS-C were included in this study. The 2017 American Heart Association guideline criteria for complete and incomplete KD were applied,[22] as well as the 2020 case definition criteria for MIS-C from the United States Centers for Disease Control and Prevention (CDC).[12] Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction (PCR) or serology; Possible if the patient had suggestive clinical features of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both; Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed.

Cardiac evaluation

Coronary artery luminal dimensions were extracted from submitted reports and converted to z scores using the body surface area adjusted regression equations from McCrindle et al.[23] For the purposes of the present analysis, only the largest z score of any branch at any time was used and categorised as normal (z score < 2), dilated (z score 2 to < 2.5), small aneurysm (z score 2.5 to < 5), medium aneurysm (z score 5 to < 10), or large or giant aneurysm (> 8 mm in diameter or z score > 10).[22] Ejection fraction was used to determine left ventricular systolic function. Left ventricular systolic function was classified as normal for left ventricular ejection fraction (LVEF) $\geq 55\%$.[24]

Statistical analysis

Data are described as frequencies, medians with interquartile range (IQR), or means with SD as appropriate to the level of measurement and distribution of the variables. The distribution of all continuous variables was plotted (box plots) in total and for each group, and visually assessed as to normality of the distribution. If the distribution was not thought to be normal, then nonparametric statistics were applied for comparisons and the median and IQR reported. Formal testing of normality was not applied. The SARS-CoV-2 infection status groups were compared with the use of Fisher exact tests, chi-square, and Mantel-Haentzel chi-square for categoric variables, Kruskal-Wallis analysis of variance for nonnormally distributed continuous variables, and analysis of variance for normally distributed continuous variables. Given the large number of comparisons that were made and the unequal size of the groups, pairwise group comparisons were not performed in order to avoid spurious findings. $P < 0.05$ was considered to be statistically significant. All analyses were performed with the use of SAS Statistical Software (version 9.4; Cary, NC) using default settings.

Results

Study population

The first MIS-C patient enrolled was hospitalised on March 29, 2020, and a total of 1708 patients were enrolled by July 18, 2022. Within a similar timeframe (March 29, 2020 to July 20, 2022), 637 KD patients were hospitalised. Thus, the study population included 2345 patients from 42 sites in 8 countries (United States 1745, Canada 257, Mexico 112, India 78, Italy 67, Egypt 54, Spain 31, Chile 1).

SARS-CoV-2 infection status

As defined in the Methods, the prior SARS-COV-2 infection status was Positive in 1541 patients (66%),

Possible in 89 (4%), Negative in 404 (17%), and Unknown in 311 (13%). For each COVID-19 status group, the proportion with a site diagnosis of KD (vs MIS-C) was 4% for Positive, 20% for Possible, 73% for Negative, and 83% for Unknown.

Patient and clinical characteristics by groups (Table 1)

The groups differed significantly in several ways, with the Positive and Possible groups and the Negative and Unknown groups appearing qualitatively to have more in common with each other. The proportion of boys ranged from 54% to 62%, with no significant differences between the groups. Age differed significantly between groups, with the Positive and Possible groups being older. Race and ethnicity also significantly varied between the groups, with the Positive group having a greater proportion of children identified as Black (278, 26%), whereas the Negative group had a greater proportion of patients identified as East Asian (29, 10%). The body mass index (BMI) z score varied significantly between the groups, with patients in the Positive and Possible groups having higher BMI z score values. Patients in the Positive group presented after symptom onset at a median of 4 days (IQR 3-6 days), Possible group 5 (3-7), Negative group 5 (4-7), and Unknown group 5 (3-6); $P < 0.001$. The clinical features of KD varied significantly among the groups, with patients in the Positive and Possible groups less likely to have extremity changes, oral mucosal changes, cervical lymphadenopathy, and skin rash compared with the Negative and Unknown groups; specifically, 64% of Positive and 54% of Possible patients had 2 KD symptoms or fewer compared with 35% of Negative and 28% of Unknown group patients (Fig. 1). Gastrointestinal symptoms (abdominal pain, diarrhea, and vomiting) differed significantly between groups, being more prevalent among the Positive and Possible groups.

Echocardiographic findings by groups (Table 2)

The degree of cardiac abnormalities varied significantly between the groups, with a greater proportion of patients in the Positive and Possible groups who developed mild or more mitral valve regurgitation, at least small pericardial effusion, and reduced LVEF (< 55%) (Fig. 2). Conversely, patients in the Negative and Unknown groups developed worse CAAs (z score ≥ 2.5) (Fig. 3), and patients in the Negative group had a higher maximum coronary artery z score than all other groups. There were no patients with giant CAAs in the Positive and Possible groups.

Clinical outcomes by groups (Table 3)

Clinical outcomes varied significantly among the groups, with a greater proportion of patients in the Positive and Possible groups presenting with shock and respiratory dysfunction, admission to intensive care , and having received respiratory support. The hospital length of stay (LOS) varied significantly among the groups, with patients in the Positive and Possible groups having longer hospital LOS. Death occurred for 6 patients (0.4%) in the Positive group, 3 (3.6%) in the Possible group, 2 (0.5%) in the Negative group, and 1 (0.3%) in the Unknown group.

Treatment by group (Table 4)

Across the groups, 90% to 97% of patients received at least 1 dose of intravenous immunoglobulin (IVIG). The proportion of patients who received therapies varied significantly among the groups, with the use of heparin, anticoagulants, interleukin blockers, inotropes, and intravenous and oral steroids being higher in the Positive and Possible groups.

Laboratory values at presentation by groups (Table 5)

Laboratory findings at presentation differed significantly among groups, with patients in the Positive and Possible groups appearing to have lower albumin, alkaline phosphatase, serum potassium, and white blood cell, lymphocyte, macrophage, eosinophil, and platelet counts. The patients in the Positive and Possible groups were also noted to have higher serum creatinine, C-reactive protein, ferritin, B-type natriuretic peptide (BNP), N-terminal pro—B-type natriuretic peptide (NT-ProBNP), and triglycerides. Fibrinogen level differed among the groups, with the patients in the Negative group having lower fibrinogen levels. Procalcitonin and troponin I levels were noted to vary significantly between the groups, with the Positive group having higher levels.

Maximal or minimal laboratory values by groups (Supplemental Table S1)

The maximal and minimal laboratory values differed significantly between the groups, with the Positive and Possible groups having a lower minimal (min) albumin, maximal (max) alkaline phosphatase, max lymphocytes, max macrophages, max eosinophils, and max platelet count. Alternatively, patients in the Positive and Possible groups had higher max aspartate transaminase, max serum creatinine, max C-reactive protein, max D-dimer, max ferritin, max BNP, max NT-ProBNP, and max triglycerides.

Discussion

Through this international prospective cohort of KD and MIS-C patients (representing the largest such analysis to date), we assessed the association of SARS-CoV-2 infection status with clinical presentation and outcomes. Clinical presentations, echocardiographic findings, treatments, laboratory values, and clinical outcomes varied significantly among the groups, with patients in the SARS-CoV-2 Positive and Possible groups presenting with more severe disease and requiring more intensive therapy, with a greater likelihood of intensive care unit admission, longer hospital LOS, and worse cardiac outcomes, including a higher likelihood of cardiac systolic dysfunction, mild or more mitral valve regurgitation, and at least small pericardial effusion, but not CAAs. Thus, these patients shared similarities with clinical descriptions of MIS-C, vs patients in the Unknown and Negative groups sharing similarities with KD. Differentiating patients based on certainty of SARS-CoV-2 infection/exposure status is therefore likely a key differentiating factor for diagnosis. These findings support the CDC decision to preserve SARS-CoV-2 exposure/disease as part of the updated 2023 diagnostic criteria for MIS-C.[15,25] However, this criterion may be increasingly difficult to apply given an increasing prevalence of

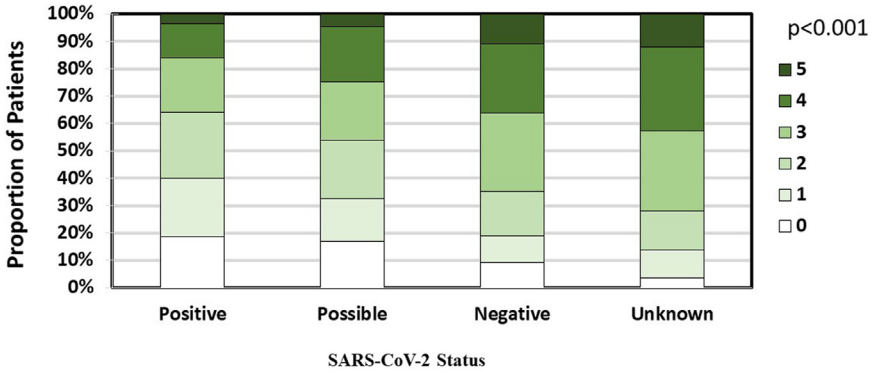

Figure 1. Number of Kawasaki disease clinical features according to SARS-CoV-2 status. Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

SARS-CoV-2 infection and vaccination in the population complicating interpretation of objective testing.

We observed multiple variations in the number and type of KD clinical features among the 4 groups. The prevalence of oral mucosal changes, cervical lymphadenopathy, and extremity changes varied significantly among the groups, with the Negative and Unknown groups having higher proportions of patients with these features (Table 1). Variations of KD features associated with the COVID-19 pandemic have been documented previously.[26-28] Burney et al. reported a reduction in the portion of KD patients presenting with classical KD clinical features (oral mucosa changes 39% vs 63% before the pandemic, lymphadenopathy 21% vs 32%, and periungual desquamation 47% vs 58%).[29] This suggests that our Negative and Unknown patients may have more in common with historical pre—COVID-19 KD patients.

The Positive and Possible groups included patients with a slightly higher BMI z score and slightly higher triglyceride levels. SARS-CoV-2 has been shown to adversely affect those with increased adiposity.[30] In addition, more severe forms of SARS-CoV-2 were associated with worse cholesterol profile. In a study of children with variable levels of severity of illness related to SARS-CoV-2, Mietus-Snyder et al. found that higher BMI, higher triglycerides, and lower high-density-lipoprotein cholesterol were associated with worse clinical manifestations.[31] Similarly, in this large cohort study of patients, those in the Positive and Possible groups who had slightly higher BMI and triglycerides had more severe presentations and developed greater ventricular dysfunction.

Children with MIS-C and KD are at risk of developing cardiac complications. Although the long-term cardiac complications in KD have been well described,[19,22] those associated with MIS-C are still being studied.[6,8,32-37] Multiple reports have described cardiac complications in MIS-C with variable frequency and severity.[9,38] In this report, we present the cardiac complications categorised by SARS-CoV-2 status in children with MIS-C or KD. Patients in the Positive and Possible groups (presumed MIS-C) had a higher likelihood of ventricular dysfunction but less severe CAAs, which is consistent with the findings of other large multicentre MIS-C registries.[39] On a similar note, patients in the Positive and Possible groups appeared to have more severe laboratory findings, which is consistent with other reports of MIS-C.[33,40]

IVIG was the most common first-line therapy used across all groups. Patients in the Positive and Possible groups, with worse clinical presentations, received more immune-modulation therapies in addition to IVIG. The optimal therapy for MIS-C remains to be determined; to our knowledge, there have been no published randomised controlled trials for the management of MIS-C.[41] Multiple clinical practice guidelines have been proposed to help front-line providers manage MIS-C patients, all endorsing IVIG as the first-line therapy in isolation or in combination with steroids.[42-46] IKDR and similar registries are best suited for future nested clinical trials to determine the efficacy of therapies, as well as to use machine learning techniques to personalise therapy and predict response.

The strengths of this paper include 1) inclusion of patients from different parts of the world encompassing both high- and low-resource countries; 2) the registry having been approved by most centres with waiver of consent, allowing the registry to bypass certain barriers to research, which was reflected in the ethnicity of the population included in the analysis: Most patients in each group were identified as non-White, which corresponds with current real-world experience[8,39]; and 3) the unique combination of validated simultaneous contemporaneous KD and MIS-C patients for comparison in the inclusion of this registry.

This study should be viewed in light of a number of limitations. Patients were not managed by a standardised protocol, and site diagnosis was not adjudicated; therefore there may be differences in clinical practice and reporting across sites and providers. It is also assumed that the sites reported all eligible patients, and the degree to which reporting may have been selective, though unlikely given reporting requirements from sites, is unknown. Another limitation may be caused by underdiagnosing or underreporting of classic KD early in the pandemic, as much as nonavailability of PCR testing for SARS-CoV-2 infection in the same period, but this cannot be verified by design of the study. A further limitation is that the DCC abstracted cardiac findings from submitted echocardiography reports, and a centralised core laboratory with a review of

Table 1. Demographics and symptoms stratified by patient groups

Item	Sub-item	Positive (n = 1541; 66%)	Possible (n = 89; 4%)	Negative (n = 404; 17%)	Unknown (n = 311; 13%)	*P* value
Male		954 (62)	48 (54)	244 (60)	184 (59)	0.41
Age at admission, y		8 (5-12)	7.6 (4-11)	3 (1-7)	3 (1-5.5)	< 0.001
Race/ethnicity		(n = 1055)	(n = 65)	(n = 281)	(n = 225)	0.001
	Black	278 (26)	4 (6)	48 (17)	30 (13)	
	Arabic	66 (6)	9 (14)	13 (5)	7 (3)	
	White	327 (31)	22 (34)	110 (39)	84 (37)	
	East Asian	9 (0.9)	2 (3)	29 (10)	7 (3)	
	Indigenous	10 (1)	1 (2)	2 (1)	3 (1)	
	Hispanic	297 (28)	24 (37)	59 (21)	71 (32)	
	South Asian	67 (6)	4 (6)	16 (6)	29 (13)	
	Southeast Asian	11 (1)	0 (0)	4 (1)	2 (1)	
	Other	30 (3)	2 (3)	18 (6)	7 (3)	
Body mass index, z score		(n = 1483) 0.6 ± 1.4	(n = 82) 0.36 ± 1.29	(n = 374) 0.12 ± 1.34	(n = 289) −0.11 ± 1.43	< 0.0001
Duration of symptoms before admission, d		(n = 1473) 4 (3-6)	(n = 87) 5 (3-7)	(n = 396) 5 (4-7)	(n = 305) 5 (3-6)	< 0.0001
Total duration of fever, d		(n = 1496) 6 (5-8)	(n = 85) 7 (5-10)	(n = 393) 7 (5-10)	(n = 305) 7 (5-10)	< 0.0001
Conjunctivitis		930 (60)	56 (63)	260 (64)	237 (76)	< 0.0001
Cervical lymphad enopathy		365 (24)	27 (30)	145 (36)	103 (33)	< 0.0001
Extremity changes		390 (25)	27 (30)	207 (51)	181 (58)	< 0.0001
Skin rash		853 (55)	52 (58)	300 (74)	244 (78)	< 0.0001
Oral mucosal changes		510 (33)	40 (45)	237 (59)	199 (64)	< 0.0001
No. of KD clinical criteria	0	287 (19)	15 (17)	38 (9)	11 (4)	< 0.001
	1	330 (21)	14 (16)	39 (10)	32 (10)	
	2	370 (24)	19 (21)	66 (16)	44 (14)	
	3	308 (20)	19 (21)	117 (29)	91 (29)	
	4	192 (12)	18 (20)	100 (25)	96 (31)	
	5	54 (4)	4 (4)	44 (11)	37 (12)	
Cough		(n = 1539) 387 (25)	(n = 89) 30 (34)	(n = 404) 117 (29)	(n = 311) 81 (26)	0.17
Sore throat		(n = 1538) 370 (24)	(n = 89) 28 (31)	(n = 403) 66 (16)	(n = 311) 48 (15)	< 0.0001
Abdominal pain		(n = 1539) 990 (64)	(n = 89) 52 (58)	(n = 404) 126 (31)	(n = 311) 73 (23)	< 0.0001
Diarrhea		(n = 1540) 737 (48)	(n = 89) 37 (42)	(n = 404) 129 (32)	(n = 311) 94 (30)	< 0.0001
Vomiting		958 (62)	58 (65)	180 (45)	120 (39)	< 0.0001
Anorexia		(n = 1514) 390 (26)	(n = 87) 20 (23)	(n = 395) 68 (17)	(n = 307) 62 (20)	0.002
Arthritis		(n = 1539) 59 (4)	(n = 89) 2 (2)	(n = 403) 28 (7)	(n = 311) 12 (4)	0.02
Myalgias		(n = 1541) 388 (25)	(n = 89) 10 (11)	(n = 403) 40 (10)	(n = 311) 21 (7)	< 0.0001
Dyspnea		(n = 1538) 263 (17)	(n = 89) 10 (11)	(n = 402) 20 (5)	(n = 310) 11 (4)	< 0.0001
Headache		(n = 1537) 567 (37)	(n = 89) 21 (24)	(n = 401) 65 (16)	(n = 310) 33 (11)	< 0.0001
Irritability		(n = 1514) 247 (16)	(n = 87) 17 (20)	(n = 395) 118 (30)	(n = 307) 110 (36)	< 0.0001
Hepatomegaly		(n = 1514) 72 (4)	(n = 87) 2 (2)	(n = 396) 10 (3)	(n = 307) 10 (3)	0.14

Results are presented as n (%), median (interquartile range), or mean ± SD. Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed.

KD, Kawasaki disease.

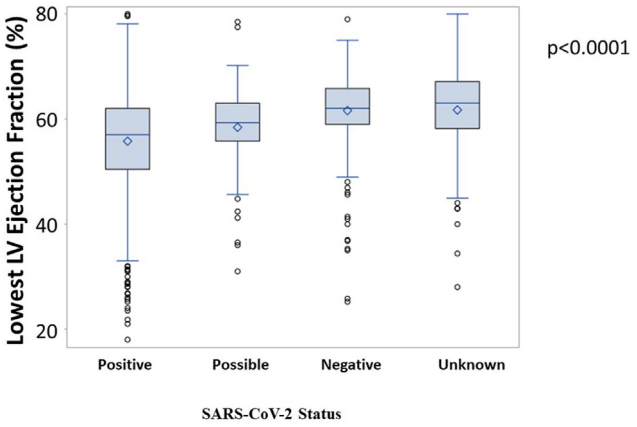

Figure 2. Lowest left ventricular (LV) ejection fraction (%) by SARS-CoV-2 status. Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

submitted recordings was not used. However, studies of the KD population have failed to show substantial differences between local and core laboratory findings, and for clinical purposes, decision making is based on local findings.[47] In this analysis, we did not include for each group how often patients met the 2017 American Heart Association KD criteria or the 2020 CDC MIS-C criteria. This is the focus of a future IKDR analysis along with factors associated with cardiac abnormalities for each condition. Finally, regarding the coronary arteries, we focused this article on the largest *z* score of any branch at any time and did not assess progression or regression. The IKDR is expected to track those patients longitudinally, and future analysis will address progression and resolution of cardiac findings, including coronary artery dilation and aneurysms, in both KD and MIS-C patients.

Conclusion

There is an overlap in presentation, management, and early outcomes between SARS-CoV-2 Positive/Possible (presumed MIS-C) and SARS-CoV-2 Negative/Unknown (presumed KD) patients, and the primary differentiating factor is history of acute SARS-CoV-2 infection or exposure. SARS-CoV-2 Positive/Possible patients had more severe clinical presentations and required more intensive management, with a greater likelihood of ventricular dysfunction but less severe coronary artery adverse outcomes. The Negative and Unknown cohort (presumed KD) closely corresponded to pre–COVID-19 KD patients. Patient recruitment continues in the IKDR, and the application of machine learning approaches to patient differentiation and prediction of optimal management pathways and response to treatment is forthcoming.

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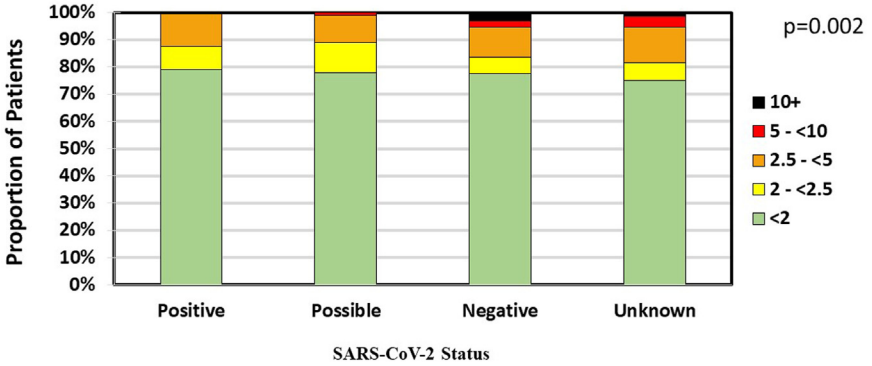

Figure 3. Coronary artery *z* score category by SARS-CoV-2 status. The largest *z* score of any branch at any time was used and categorised as normal (*z* score < 2), dilated (*z* score 2 to < 2.5), small aneurysm (*z* score 2.5 to < 5), medium aneurysm (*z* score 5 to < 10), or large aneurysm (> 8 mm in diameter or *z* score > 10).[22] Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Echocardiogram findings stratified by patient group

Item	Sub-item	Positive (n = 1541; 66%)	Possible (n = 89; 4%)	Negative (n = 404; 17%)	Unknown (n = 311; 13%)	*P* value
Maximum RCA *z* score (continuous variable)		(n = 1324) 0.77 (−0.03 to 1.54)	(n = 67) 0.84 (0.15-1.76)	(n = 368) 1.02 (0.4-1.7)	(n = 246) 0.76 (0.02-1.5)	0.0006
Maximum LMCA *z* score (continuous variable)		(n = 1275) 0.61 (−0.13 to 1.33)	(n = 66) 0.52 (0.07-1.08)	(n = 366) 0.83 (0.16-1.57)	(n = 246) 0.47 (−0.30 to 1.26)	0.36
Maximum LAD *z* score (continuous variable)		(n = 1246) 0.78 (−0.03 to 1.51)	(n = 66) 0.59 (−0.05 to 1.19)	(n = 363) 0.56 (0.01-1.29)	(n = 220) 0.61 (−0.11 to 1.6)	0.14
Maximum circumflex coronary artery *z* score (continuous variable)		(n = 803) −0.57 (−1.48 to 0.34)	(n = 48) −0.17 (−1.27 to 0.39)	(n = 283) −0.47 (−1.33 to 0.51)	(n = 171) −0.28 (−1.20 to 0.53)	0.07
Maximum coronary artery *z* score in any branch at any timepoint		(n = 1485) 1.18 (0.33-1.86)	(n = 82) 0.95 (0.00-1.76)	(n = 398) 1.34 (0.68-1.91)	(n = 265) 1.16 (0.36-1.99)	0.02
Degree of ventricular dysfunction		(n = 1300)	(n = 75)	(n = 354)	(n = 204)	< 0.0001
	LVEF ≥ 55%	808 (62)	57 (76)	323 (91)	171 (84)	
	LVEF 40%-54%	406 (31)	15 (20)	25 (7)	31 (15)	
	LVEF ≤ 40%	86 (7)	3 (4)	6 (2)	2 (1)	
LVEF, % (continuous variable)		(n = 1300) 57 (50.4-62)	(n = 75) 59.6 (55.8-63)	(n = 354) 62 (59-65.8)	(n = 204) 63 (58.4-67.4)	< 0.0001
Mitral valve regurgitation grade		(n = 1330)	(n = 64)	(n = 361)	(n = 225)	< 0.0001
	None	1024 (77)	50 (78)	327 (91)	210 (93)	
	Mild	262 (20)	13 (20)	27 (7)	12 (5)	
	Moderate	42 (3)	1 (2)	7 (2)	3 (1)	
	Severe	2 (0.2)	0 (0)	0 (0)	0 (0)	
Pericardial effusion grade		(n = 1337)	(n = 65)	(n = 360)	(n = 225)	0.04
	None	1201 (90)	59 (91)	336 (93)	213 (95)	
	Small	133 (10)	6 (9)	24 (7)	11 (5)	
	Moderate	3 (0.2)	0 (0)	0 (0)	0 (0)	
	Large	0 ()	0 (0)	0 (0)	1 (0.4)	

Results are presented as median (interquartile range) or n (%). Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed.

LAD, left anterior descending coronary artery; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; RCA, right coronary artery.

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Table 3. Clinical outcomes stratified by patient group

Item	Sub-item	Positive (n = 1541; 66%)	Possible (n = 89; 4%)	Negative (n = 404; 17%)	Unknown (n = 311; 13%)	*P* value
Admitted to ICU		(n = 1538)	(n = 89)	(n = 404)	(n = 311)	< 0.0001
		844 (55)	37 (42)	55 (14)	49 (16)	
Shock		(n = 1537)	(n = 89)	(n = 402)	(n = 309)	< 0.0001
		498 (32)	29 (33)	25 (6)	14 (5)	
Cardiac arrest/failure		(n = 1535)	(n = 89)	(n = 403)	(n = 311)	0.04
		40 (3)	3 (3)	5 (1)	2 (0.6)	
Arrhythmia		(n = 1535)	(n = 89)	(n = 402)	(n = 310)	0.0003
		112 (7)	7 (8)	12 (3)	9 (3)	
Respiratory support		(n = 1537)	(n = 89)	(n = 402)	(n = 302)	< 0.0001
		568 (37)	21 (24)	42 (10)	19 (6)	
Respiratory dysfunction*		(n = 1532)	(n = 88)	(n = 401)	(n = 302)	< 0.0001
	None	999 (65)	64 (73)	349 (87)	280 (93)	
	Moderate	373 (24)	16 (18)	43 (11)	21 (7)	
	Severe	160 (10)	8 (9)	9 (2)	1 (0.33)	
Renal dysfunction†		(n = 1534)	(n = 89)	(n = 403)	(n = 311)	< 0.0001
		132 (9)	2 (2)	11 (3)	1 (0.3)	
Total hospital length of stay, d		7 (5-10)	6 (4-8)	5 (4-8)	5 (4-8)	< 0.0001
Total duration of initial ICU stay, d		(n = 842)	(n = 37)	(n = 55)	(n = 49)	0.37
		3 (2-5)	3 (2-6)	2 (1-5)	3 (2-5)	
Hospital readmission		(n = 1526)	(n = 88)	(n = 403)	(n = 310)	< 0.0001
		57 (3.74)	7 (7.95)	26 (6.45)	32 (10.32)	

Results are presented as n (%) or median (IQR). Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed.

ICU, intensive care unit.

* Respiratory dysfunction was defined as none if O_2 saturation was > 93% on room air, with no dyspnea nor abnormal chest imaging, moderate if there was tachypnea with or without hypoxia (O_2 saturation ≤ 93% on room air) and abnormal chest imaging with < 50% involvement of the lung parenchyma, and severe if there was tachypnea with hypoxia (O_2 saturation ≤ 93% on room air or PaO_2/FiO_2 < 300 mm Hg) and > 50% involvement of the lung parenchyma on chest imaging.

† Renal dysfunction was defined as acute kidney injury or need for continuous renal replacement therapy.

Table 4. Treatments stratified by patient group

Item	Sub-item	Positive (n = 1541; 66%)	Possible (n = 89; 4%)	Negative (n = 404; 17%)	Unknown (n = 311; 13%)	*P* value
No. of IVIG doses		(n = 1539)	(n = 89)	(n = 404)	(n = 311)	0.01
	0	89 (6)	5 (6)	40 (10)	9 (3)	
	1	1283 (83)	79 (89)	320 (79)	260 (84)	
	2	164 (11)	4 (4)	43 (11)	41 (13)	
	3	2 (0.1)	1 (1)	1 (0.3)	1 (0.3)	
	4	1 (0.1)	0	0	0	
IVIG resistant		(n = 1448)	(n = 84)	(n = 363)	(n = 301)	0.40
		174 (12)	8 (10)	53 (15)	42 (14)	
No. of days between hospital admission and first IVIG		(n = 1540)	(n = 84)	(n = 363)	(n = 301)	0.001
		1 (0-1)	0 (0-1)	1 (0-1)	1 (0-1)	
Intravenous steroids		(n = 1539)	(n = 89)	(n = 403)	(n = 310)	< 0.0001
		1182 (77)	57 (64)	151 (37)	93 (30)	
Oral steroids		(n = 1533)	(n = 89)	(n = 404)	(n = 311)	< 0.0001
		927 (60)	41 (46)	147 (36)	86 (28)	
TNF-α inhibitor (eg, infliximab, etanercept)		(n = 1538)	(n = 89)	(n = 404)	(n = 311)	0.30
		88 (6)	1 (1)	24 (6)	16 (5)	
IL-1 blocker (eg, anakinra)		(n = 1539)	(n = 89)	(n = 404)	(n = 311)	< 0.0001
		277 (18)	9 (10)	22 (5)	15 (5)	
Antiplatelet therapy		(n = 1541)	(n = 89)	(n = 404)	(n = 310)	< 0.0001
		1228 (80)	67 (75)	353 (87)	287 (93)	
Unfractionated heparin		(n = 1539)	(n = 89)	(n = 404)	(n = 310)	< 0.0001
		177 (12)	10 (11)	9 (2)	2 (1)	
Anticoagulants		(n = 1540)	(n = 89)	(n = 404)	(n = 311)	< 0.0001
		795 (52)	25 (28)	71 (18)	33 (11)	
Direct oral anticoagulant		(n = 1529)	(n = 89)	(n = 403)	(n = 310)	< 0.0001
		103 (7)	2 (2)	6 (1)	0	
NSAIDs		(n = 1536)	(n = 89)	(n = 402)	(n = 309)	< 0.0001
		572 (37)	28 (31)	110 (27)	72 (23)	
Inotropes		(n = 1540)	(n = 89)	(n = 404)	(n = 311)	< 0.0001
		647 (41)	26 (29)	81 (20)	27 (9)	
Diuretics		211(14)	5 (6)	11(3)	8 (3)	< 0.0001
Antivirals		(n = 1538)	(n = 89)	(n = 404)	(n = 311)	0.0001
		47 (3)	1 (1)	1 (0.3)	0	
Antibiotics		459 (30)	13 (15)	77 (19)	56 (18)	< 0.0001

Results are presented as n (%) or median (IQR). Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed.

IL, interleukin; IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug; TNF, tumour necrosis factor.

Table 5. Laboratory values at presentation stratified by patient group

Item	Positive (n = 1541; 66%)	Possible (n = 89; 4%)	Negative (n = 404; 17%)	Unknown (n = 311; 13%)	*P* value
Albumin, g/L	(n = 1255) 32 (27-37)	(n = 69) 31 (27-36)	(n = 336) 34 (29-38)	(n = 209) 34 (30-39)	< 0.0001
Alkaline phosphatase, U/L	(n = 1124) 141 (108-187.5)	(n = 46) 149 (111-187)	(n = 205) 173 (138-225)	(n = 174) 180 (141-227)	< 0.0001
Alanine transferase, U/L	(n = 1188) 39 (27-62)	(n = 55) 33 (25-54)	(n = 243) 41 (29-64)	(n = 191) 35 (26-60)	0.15
Aspartate transaminase, U/L	(n = 1236) 31 (19-53)	(n = 69) 22 (14-55)	(n = 293) 27 (17-60)	(n = 222) 25.5 (15-71)	0.11
GGT, U/L	(n = 332) 34.5 (21-71.5)	(n = 26) 37 (20-64)	(n = 111) 28 (14-63)	(n = 88) 38 (15.5-85)	0.06
Total bilirubin, μmol/L	(n = 1234) 9.85 (6.84-15.39)	(n = 65) 7.9 (5.13-11.97)	(n = 225) 7.7 (5.13-10.26)	(n = 194) 6.84 (5.13-10.26)	< 0.0001
Direct bilirubin, μmol/L	(n = 589) 3.42 (1.71-6.84)	(n = 46) 3.42 (2.4-5)	(n = 126) 3 (1.4-5.13)	(n = 100) 3.42 (1.71-3.42)	0.005
Amylase, U/L	(n = 1421) 54 (33-76.5)	(n = 4) 51 (25.5-83.5)	(n = 16) 54.5 (37.50-86)	(n = 20) 44.5 (41-64.5)	0.69
Blood urea nitrogen, mmol/L	(n = 1230) 4.28 (3.21-6.43)	(n = 57) 3.93 (2.86-5)	(n = 223) 3.21 (2.5-4.28)	(n = 168) 3.59 (2.5-5.36)	< 0.0001
Creatinine, μmol/L	(n = 1281) 45.08 (33.6-61.88)	(n = 72) 43.5 (32.86-61.89)	(n = 268) 30.94 (22.54-41.56)	(n = 202) 27.2 (20.34-38.01)	< 0.0001
Sodium, mmol/L	(n = 1322) 134 (132-137)	(n = 74) 135 (133-138)	(n = 363) 136 (134-138)	(n = 230) 135 (133-137)	< 0.0001
Chloride, mmol/L	(n = 1256) 101.5 (98-105)	(n = 69) 100 (98-105)	(n = 304) 103 (100-105)	(n = 208) 102 (99-105)	0.0003
Potassium, mmol/L	(n = 1309) 3.9 (3.5-4.3)	(n = 74) 3.95 (3.5-4.2)	(n = 356) 4.3 (3.9-4.8)	(n = 214) 4.2 (3.8-4.7)	< 0.0001
Bicarbonate, mmol/L,	(n = 896) 21 (19-24)	(n = 32) 21 (18.6-23)	(n = 153) 22 (20-24)	(n = 156) 21 (19-24)	0.27
Erythrocyte sedimentation rate, mm/h	(n = 869) 46 (30-70)	(n = 50) 50.5 (33-60)	(n = 203) 51 (30-73)	(n = 148) 60 (33.5-83.5)	0.005
C-reactive protein, mg/L	(n = 1187) 140 (71-213.9)	(n = 64) 122.18 (59.5-211.45)	(n = 223) 83.5 (41-156.5)	(n = 222) 86.6 (41.2-151)	< 0.0001
d-Dimer, μg/mL DDU	(n = 1246) 1.44 (0.83-2.13)	(n = 60) 1 (0.53-1.79)	(n = 238) 0.84 (0.47-1.81)	(n = 144) 0.86 (0.46-1.62)	< 0.0001
Ferritin, μg/L	(n = 1260) 385.5 (212.65-733.45)	(n = 70) 283.25 (167.4-602.6)	(n = 290) 183.5 (115.6-333.9)	(n = 156) 184.5 (101.5-302.5)	< 0.0001
Fibrinogen, g/L	(n = 986) 5.2 (4.19-6.33)	(n = 56) 5.1 (4.28-6.33)	(n = 226) 4.8 (3.3-6.2)	(n = 124) 5.5 (4.54-6.8)	0.0005
Procalcitonin, μg/L	(n = 422) 4.04 (1.55-13.21)	(n = 15) 1.6 (0.2-8)	(n = 34) 1.03 (0.44-3.5)	(n = 46) 1.34 (0.6-3.5)	< 0.0001
Lactate dehydrogenase, U/L	(n = 1002) 363 (269-605)	(n = 52) 271.5 (231-467.5)	(n = 176) 426.5 (288-665)	(n = 125) 374 (266-559)	0.002
BNP, ng/L	(n = 463) 176 (32.6-564)	(n = 19) 288 (58-729)	(n = 43) 118 (14-395)	(n = 65) 104 (36-234)	0.02
NT-ProBNP, ng/L	(n = 526) 2349 (479-8600)	(n = 43) 855 (452-3378)	(n = 120) 321.2 (129.5-1249)	(n = 60) 649.5 (255.5-3047.5)	< 0.0001
HS troponin I, ng/L*	(n = 111) 34 (9.99-140)	(n = 17) 39 (16-78)	(n = 25) 14 (4-25)	(n = 22) 7.5 (4.72-21)	0.002
Troponin I, ng/L*	(n = 712) 15 (5.35-80.9)	(n = 34) 10.65 (2.7-61)	(n = 138) 9.99 (9.99-11.4)	(n = 95) 10 (4.5-17)	< 0.0001
Red blood cell count, $\times 10^{12}$/L)	(n = 1299) 4.14 (3.75-4.52)	(n = 69) 4.11 (3.87-4.49)	(n = 386) 4.17 (3.79-4.5)	(n = 246) 3.14 (3.76-4.39)	0.46
Hemoglobin, g/L	(n = 1371) 113 (102-124)	(n = 74) 110 (102-120)	(n = 388) 110 (101-120)	(n = 246) 109 (100-119)	0.002
White blood cell count, $\times 10^9$/L	(n = 1260) 9.7 (6.9-13.7)	(n = 79) 10.3 (7.7-15.3)	(n = 389) 12.3 (8.7-17.36)	(n = 247) 13.02 (9.2-17.2)	< 0.0001
Neutrophils, $\times 10^9$/L	(n = 1226) 7.2 (4.7-10.69)	(n = 74) 7.57 (4.5-12.92)	(n = 353) 7.43 (4.2-10.7)	(n = 189) 8 (5.04-11.6)	0.29
Lymphocytes, $\times 10^9$/L	(n = 1175) 1.11 (0.65-1.93)	(n = 73) 1.36 (0.8-2.4)	(n = 349) 2.81 (1.42-4.7)	(n = 184) 2.6 (1.4-4.12)	< 0.0001
Macrophages, $\times 10^9$/L	(n = 1124) 0.38 (0.2-0.64)	(n = 65) 0.5 (0.2-0.83)	(n = 340) 0.75 (0.4-1.2)	(n = 173) 0.7 (0.4-1.11)	< 0.0001
Eosinophils, $\times 10^9$/L	(n = 995) 0.1 (0.01-0.22)	(n = 65) 0.1 (0-0.22)	(n = 218) 0.15 (0.02-0.42)	(n = 160) 0.19 (0.02-0.4)	< 0.0001
Basophils, $\times 10^9$/L	(n = 970) 0.01 (0-0.03)	(n = 60) 0 (0-0.02)	(n = 287) 0.03 (0-0.08)	(n = 147) 0.01 (0-0.06)	< 0.0001
Platelet count, $\times 10^9$/L	(n = 1168) 180 (126-263)	(n = 75) 242 (134-332)	(n = 325) 323 (213-424)	(n = 240) 347 (238-465)	< 0.0001

Table 5. Continued.

Item	Positive (n = 1541; 66%)	Possible (n = 89; 4%)	Negative (n = 404; 17%)	Unknown (n = 311; 13%)	*P* value
Prothrombin time, s	(n = 825) 14.9 (13.8-16.2)	(n = 49) 14.7 (14-15.9)	(n = 118) 14.1 (13-15.1)	(n = 113) 14.1 (13.3-15.2)	< 0.0001
Partial thromboplastin time, s	(n = 850) 33 (29.7-37.3)	(n = 55) 33.3 (30.9-38.5)	(n = 148) 31 (27.15-35)	(n = 114) 31.4 (28-35)	< 0.0001
INR	(n = 837) 1.2 (1.1-1.34)	(n = 53) 1.17 (1.02-1.34)	(n = 142) 1.13 (1.07-1.2)	(n = 110) 1.2 (1.08-1.3)	< 0.0001
Triglycerides, μmol/L	(n = 477) 1.82 (1.29-2.6)	(n = 35) 1.84 (1.11-2.31)	(n = 167) 1.62 (1.16-2.19)	(n = 48) 1.52 (1.12-1.89)	0.04

Results are presented as n (%) or median (interquartile range). Patients were stratified by SARS-CoV-2 infection status into 4 groups: Positive if the patient had a confirmed household contact within the 4 weeks before the onset of symptoms or a positive test via polymerase chain reaction [PCR], serology, or both, Possible if the patient had clinical features suggestive of MIS-C or KD without household contact and with only 1 negative test, either PCR or serology but not both, Negative if the patient had no exposure and had both negative PCR and negative serology, and Unknown if the patient had no known exposure and PCR and serology testing were not performed.

BNP, B-type natriuretic peptide; DDU, di-dimer units; GGT, gamma-glutamyl transferase; HS, high-sensitivity; IL, Interleukin; INR, international normalization ratio; NT-ProBNP, N-terminal pro—B-type natriuretic peptide.

*For patients with HS troponin I or troponin I values reported < 10 (below the detectable range), a value of 9.99 was arbitrarily entered.

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Data Availability

Data will be available upon a reasonable request.

Ethics Statement

The International KD Registry (IKDR) protocols were approved by participating centres with informed consent or waiver of consent depending on jurisdiction. Depending on jurisdiction and when required, the authors confirm that patient consent forms were obtained for this article.

Patient Consent

The International KD Registry (IKDR) protocols were approved by participating centres with informed consent or waiver of consent depending on jurisdiction. Depending on jurisdiction and when required, the authors confirm that patient consent forms were obtained for this article.

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Disclosures

Dr Harahsheh serves as a scientific advisory board member of OP2 DRUGS. This advisory position has no relevance for the present report. The other authors have no conflicts of interest to disclose.

References

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. Arerugi 1967;16:178-222 [in Japanese].
2. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: is there a linkage to Kawasaki disease? Trends Cardiovasc Med 2020;30:389-96.
3. Hara T, Furuno K, Yamamura K, et al. Assessment of pediatric admissions for kawasaki disease or infectious disease during the COVID-19 state of emergency in Japan. JAMA Netw Open 2021;4:e214475.
4. Elias MD, McCrindle BW, Larios G, et al. Management of multisystem inflammatory syndrome in children associated with COVID-19: a survey from the International Kawasaki Disease Registry. CJC Open 2020;2:632-40.
5. Harahsheh AS, Sharron MP, Bost JE, et al. Comparison of first and second wave cohorts of multisystem inflammatory disease syndrome in children. Pediatr Infect Dis J 2022;41:e21-5.
6. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324:259-69.
7. Lamrani L, Manlhiot C, Elias MD, et al. Kawasaki disease shock syndrome vs classical Kawasaki disease: a meta-analysis and comparison with SARS-CoV-2 multisystem inflammatory syndrome. Can J Cardiol 2021;37:1619-28.
8. Harahsheh AS, Krishnan A, DeBiasi RL, et al. Cardiac echocardiogram findings of severe acute respiratory syndrome coronavirus-2—associated multi-system inflammatory syndrome in children. Cardiol Young 2020;32:727.
9. Hejazi OI, Loke YH, Harahsheh AS. Short-term cardiovascular complications of multi-system inflammatory syndrome in children (MIS-C) in adolescents and children. Curr Pediatr Rep 2021;9:93-103.
10. Lin J, Harahsheh AS, Raghuveer G, et al. Emerging insights into the pathophysiology of multi-system inflammatory syndrome in children associated with COVID-19. Can J Cardiol 2023;39:793-802.

11. Ghosh P, Katkar GD, Shimizu C, et al. An artificial intelligence—guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. Nat Commun 2022;13:2687.

12. Centers for Disease Control and Prevention: Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed May 16, 2020.

13. World Health Organisation: Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed May 16, 2020.

14. Royal College of Paediatrics and Child Health: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS)—guidance for clinicians. Available at: https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance. Accessed May 10, 2020.

15. Centers for Disease Control and Prevention: Information for healthcare providers about multisystem inflammatory syndrome in children-2023 case defintion update. Available at: https://www.cdc.gov/mis/mis-c/hcp_cstecdc/index.html. Accessed January 30, 2023.

16. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005;191:499-502.

17. Low T, McCrindle BW, Mueller B, et al. Associations between the spatiotemporal distribution of Kawasaki disease and environmental factors: evidence supporting a multifactorial etiologic model. Sci Rep 2021;11:14617.

18. Manlhiot C, Newburger JW, Low T, et al. Low-molecular-weight heparin vs warfarin for thromboprophylaxis in children with coronary artery aneurysms after Kawasaki disease: a pragmatic registry trial. Can J Cardiol 2020;36:1598-607.

19. McCrindle BW, Manlhiot C, Newburger JW, et al. Medium-term complications associated with coronary artery aneurysms after Kawasaki disease: a study from the International Kawasaki Disease Registry. J Am Heart Assoc 2020;9:e016440.

20. Osborne J, Friedman K, Runeckles K, et al. Comparison between currently recommended long-term medical management of coronary artery aneurysms after Kawasaki disease and actual reported management in the last two decades. Pediatr Cardiol 2021;42:676-84.

21. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.

22. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-99.

23. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 2007;116:174-9.

24. Margossian R, Schwartz ML, Prakash A, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging measurements of functional single ventricular volumes, mass, and ejection fraction (from the Pediatric Heart Network Fontan Cross-Sectional Study). Am J Cardiol 2009;104:419-28.

25. Son MBF, Burns JC, Newburger JW. A new definition for multisystem inflammatory syndrome in children. Pediatrics 2023;151:e2022060302.

26. Toubiana J, Cohen JF, Brice J, et al. Distinctive features of Kawasaki disease following SARS-CoV-2 infection: a controlled study in Paris, France. J Clin Immunol 2021;41:526-35.

27. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395(10239):1771-8.

28. Fernandez-Cooke E, Grasa CD, Dominguez-Rodriguez S, et al. Prevalence and clinical characteristics of SARS-CoV-2 confirmed and negative Kawasaki disease patients during the pandemic in Spain. Front Pediatr 2020;8:617039.

29. Burney JA, Roberts SC, DeHaan LL, et al. Epidemiological and clinical features of Kawasaki disease during the COVID-19 pandemic in the United States. JAMA Netw Open 2022;5:e2217436.

30. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.

31. Mietus-Snyder M, Suslovic W, Delaney M, et al. Changes in HDL cholesterol, particles, and function associate with pediatric COVID-19 severity. Front Cardiovasc Med 2022;9:1033660.

32. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142:429-36.

33. DeBiasi RL, Harahsheh AS, Srinivasalu H, et al. Multisystem inflammatory syndrome of children: sub-phenotypes, risk factors, biomarkers, cytokine profiles and viral sequencing. J Pediatr 2021;237:125-135.e18.

34. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347-58.

35. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020;383:334-46.

36. Matsubara D, Kauffman HL, Wang Y, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol 2020;76:1947-61.

37. Aeschlimann FA, Misra N, Hussein T, et al. Myocardial involvement in children with post-COVID multisystem inflammatory syndrome: a cardiovascular magnetic resonance based multicenter international study—the CARDOVID registry. J Cardiovasc Magn Reson 2021;23:140.

38. Alsaied T, Tremoulet AH, Burns JC, et al. Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation 2021;143:78-88.

39. Belay ED, Abrams J, Oster ME, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr 2021;175:837-45.

40. Fridman MD, Tsoukas P, Jeewa A, et al. Differentiation of COVID-19—associated multisystem inflammatory syndrome from Kawasaki disease with the use of cardiac biomarkers. Can J Cardiol 2022;39:815-23.

41. Channon-Wells S, Vito O, McArdle AJ, et al. Immunoglobulin, glucocorticoid, or combination therapy for multisystem inflammatory syndrome in children: a propensity-weighted cohort study. Lancet Rheumatol 2023;5:e184-99.

42. Harahsheh AS, Portman MA, Khoury M, et al. Management of multisystem inflammatory syndrome in children: decision-making regarding a new condition in the absence of clinical trial data. Can J Cardiol 2023;39:803-14.

43. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 3. Arthritis Rheumatol 2022;74:e1-20.

44. Schlapbach LJ, Andre MC, Grazioli S, et al. Best practice recommendations for the diagnosis and management of children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS; multisystem inflammatory syndrome in children, MIS-C) in Switzerland. Front Pediatr 2021;9:667507.

45. Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. Lancet Child Adolesc Health 2021;5:133-41.

46. Cattalini M, Taddio A, Bracaglia C, et al. Childhood multisystem inflammatory syndrome associated with COVID-19 (MIS-C): a diagnostic and treatment guidance from the Rheumatology Study Group of the Italian Society of Pediatrics. Ital J Pediatr 2021;47:24.

47. Margossian R, Lu M, Minich LL, et al. Predictors of coronary artery visualization in Kawasaki disease. J Am Soc Echocardiogr 2011;24:53-9.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2023.06.001.

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