Title

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

Authors

Harahsheh, Ashraf
Shah, Samay
Dallaire, Frederic
et al.

Publication Date

2023-06-07

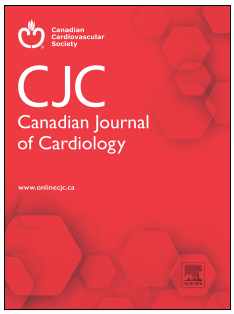
DOI

10.1016/j.cjca.2023.06.001

Peer reviewed

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



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

Ashraf S. Harahsheh, M.D., F.A.C.C., F.A.A.P, Samay Shah, MS, Frederic Dallaire, MD, Cedric Manlhiot, PhD, Michael Khoury, MD, Simon Lee, MD, Marianna Fabi, MD, Daniel Mauriello, MD, Elif Seda Selamet Tierney, MD, Arash A. Sabati, MD, Audrey Dionne, MD, Nagib Dahdah, MD, MBA, Nadine Choueiter, MD, Deepika Thacker, MD, Therese M. Giglia, MD, Dongngan T. Truong, MD, MS, Supriya Jain, MD, Michael Portman, MD, William B. Orr, MD, Tyler H. Harris, MD, Jacqueline R. Szmuszkovicz, MD, Pedrom Farid, BMSc, Brian W. McCrindle, MD, MPH, on behalf of the International Kawasaki Disease Registry (IKDR)

PII: S0828-282X(23)00451-8

DOI: https://doi.org/10.1016/j.cjca.2023.06.001

Reference: CJCA 4680

To appear in: *Canadian Journal of Cardiology*

Received Date: 27 April 2023

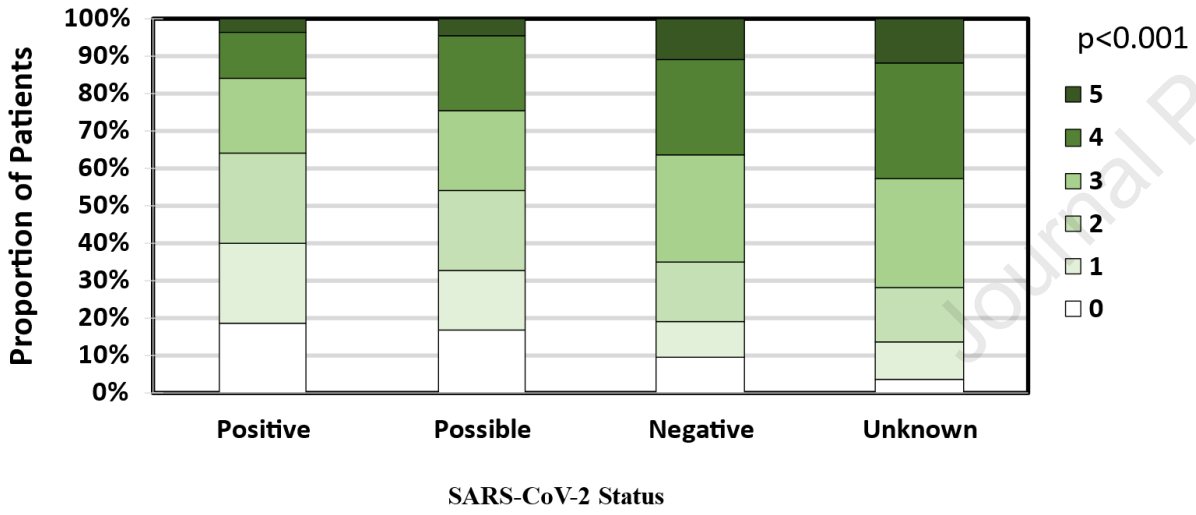
Revised Date: 31 May 2023

Accepted Date: 1 June 2023

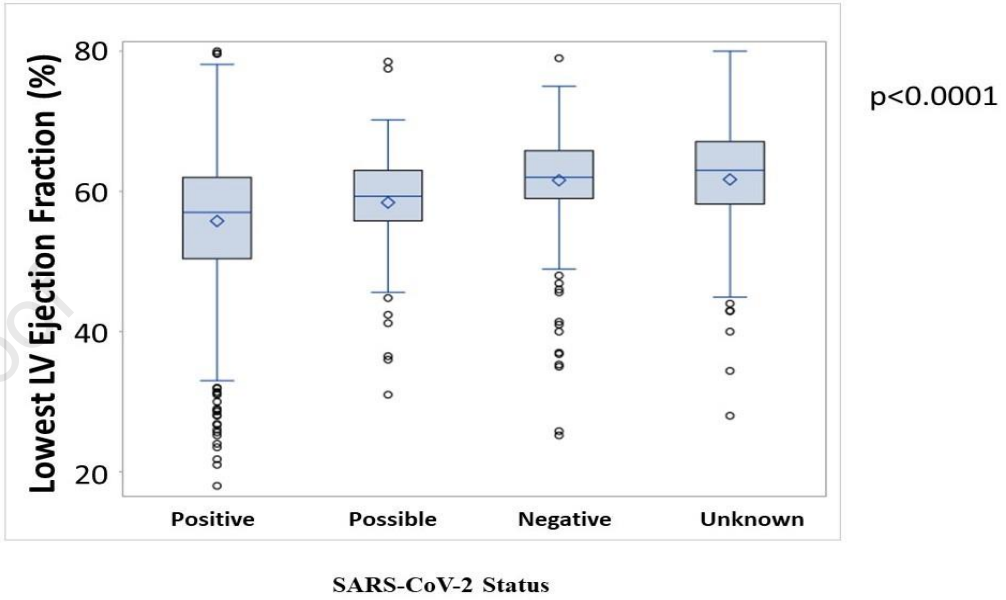
Please cite this article as: Harahsheh AS, Shah S, Dallaire F, Manlhiot C, Khoury M, Lee S, Fabi M, Mauriello D, Selamet Tierney ES, Sabati AA, Dionne A, Dahdah N, Choueiter N, Thacker D, Giglia TM, Truong DT, Jain S, Portman M, Orr WB, Harris TH, Szmuszkovicz JR, Farid P, McCrindle BW, on behalf of the International Kawasaki Disease Registry (IKDR), Kawasaki Disease in the Time of COVID-19 and MIS-C – The International Kawasaki Disease Registry *Canadian Journal of Cardiology* (2023), doi: https://doi.org/10.1016/j.cjca.2023.06.001.

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.

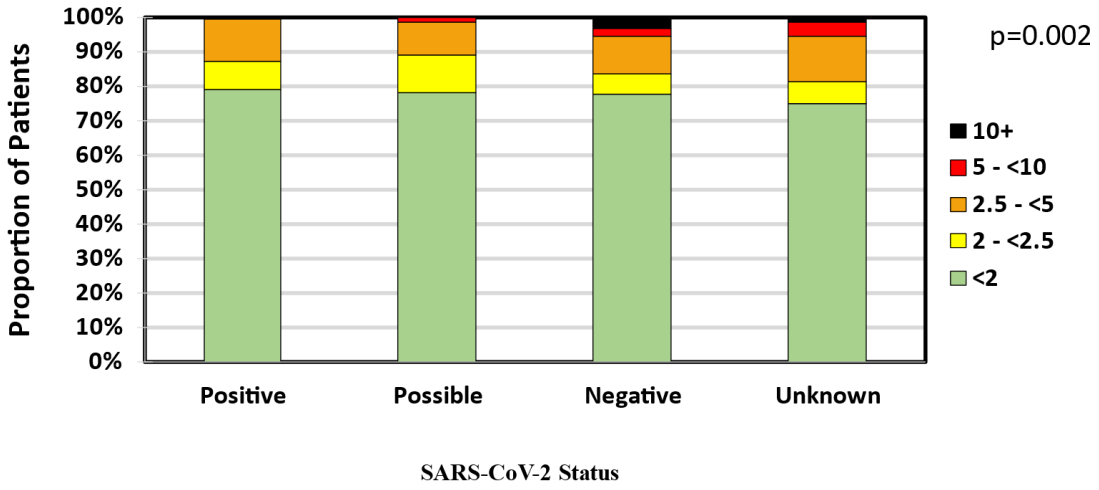
Number of Kawasaki Disease Clinical Features by SARS-CoV-2 Status



Lowest Left Ventricular Ejection Fraction by SARS-CoV-2 Status



Coronary Artery z-Score Category by SARS-CoV-2 Status



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.

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

Short title: Kawasaki Disease in the Time of COVID-19 and MIS-C

Ashraf S. Harahsheh, M.D., F.A.C.C., F.A.A.P.[1]; Samay Shah, MS[2]; Frederic Dallaire, MD[3], Cedric Manlhiot, PhD[4], Michael Khoury, MD[5], Simon Lee, MD[6], Marianna Fabi, MD[7], Daniel Mauriello, MD[8], Elif Seda Selamet Tierney, MD[9], Arash A. Sabati, MD[10], Audrey Dionne, MD[11], Nagib Dahdah, MD, MBA[12], Nadine Choueiter, MD[13], Deepika Thacker, MD[14], Therese M. Giglia, MD[15], Dongngan T. Truong, MD, MS[16], Supriya Jain, MD[17], Michael Portman, MD[18], William B. Orr, MD[19], Tyler H. Harris, MD[20], Jacqueline R. Szmuszkovicz, MD[21], Pedrom Farid, BMSc[22], Brian W McCrindle MD, MPH[22], on behalf of the International Kawasaki Disease Registry (IKDR)*

[1] Division of Cardiology, Department of Pediatrics, Children's National Hospital; George Washington University School of Medicine & Health Sciences; 111 Michigan Ave, NW Washington, DC 20010, USA

[2] Medical student at George Washington University School of Medicine & Health Sciences, Washington, DC

[3] Department of pediatrics, Université de Sherbrooke, and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada

[4] Blalock-Taussig-Thomas Congenital Heart Center at Johns Hopkins University, Baltimore, MD, USA

[5] Division of Pediatric Cardiology, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

[6] The Heart Center at Nationwide Children's Hospital, Columbus, OH, USA

[7] Pediatric Emergency Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy

[8] Johns Hopkins All Children's Hospital, Saint Petersburg, FL, USA

[9] Department of Pediatrics, Division of Cardiology, Lucile Packard Children's Hospital, Stanford University Medical Center, Palo Alto, CA, USA

[10] Phoenix Children's Hospital, Phoenix, AZ, USA

[11] Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

[12] Division of Pediatric Cardiology, CHU Ste-Justine, University of Montreal, Montreal, QC, Canada

[13] Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA

[14] Nemours Children's Hospital, Wilmington, DE, USA

[15] Children's Hospital of Philadelphia, Philadelphia, PA, USA

[16] University of Utah and Primary Children's Hospital, Salt Lake City, UT, USA

[17] New York Medical College/Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, NY, USA

[18] Seattle Children's Hospital, Seattle, WA, USA

[19] Division of Pediatric Cardiology, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA

[20] UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

[21] Children's Hospital of Los Angeles, Los Angeles, CA, USA

[22] Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada

***Authors from the International Kawasaki Disease Registry:**

Mahmoud Alsalehi (Kingston Health Science Centre, Kingston, ON, Canada), Jean A. Ballweg (Children's Hospital and Medical Center. University of Nebraska Medical Center, Omaha NE), Benjamin Barnes (Johns Hopkins School of Medicine, Baltimore MD, USA), Elizabeth Braunlin (University of Minnesota, Minneapolis, MN, USA), Ashley Buffone (Division of Pediatric Cardiology, CHU Ste-Justine, University of Montreal, Montreal, QC, Canada), Juan Carlos Bustamante-Ogando (Hospital Angeles Lomas, Huixquilucan, Mexico), Athur J. Chang (Jacobs School of Medicine and BioMedical Sciences, University at Buffalo, Buffalo, NY, USA), Nicolas Corral (Childrens Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY, USA), Paul Dancey (Janeway Children's Health and Rehabilitation Centre, Saint John's, NL, Canada), Mona El-Ganzoury (Pediatric Cardiology Division, Department of Pediatrics, Ain-Shams University, Cairo, Egypt), Nora El-Samman (Pediatric Cardiology Division, Department of Pediatrics, Ain-Shams University, Cairo, Egypt), Matthew Elias (Children's Hospital of Philadelphia, Philadelphia, PA, USA), Elisa Fernandez-Cooke (Hospital 12 de Octubre (Imas12), Madrid, Spain), Kevin Friedman (Boston Children's Hospital, Harvard Medical School, Boston, MA, USA), Luis Martin Garrido-Garcia (Instituto Nacional de Pediatría,. Mexico City, Mexico), Luis Martin Garrido (Hospital Angeles Lomas, Huixquilucan, Mexico), Guillermo Larios Goldenberg (Hospital Clínico UC-Christus, Pontificia Universidad Católica de Chile, Santiago, Chile), Michelle M. Grcic (The Heart Center at Nationwide Children's Hospital, Columbus, OH, USA), Kevin C. Harris (Children's Heart Centre, BC Children's Hospital and University of British Columbia, Vancouver, BC, Canada.), Mark D. Hicar (Jacobs School of Medicine and BioMedical Sciences, University at Buffalo, Buffalo, NY, USA), Bridgette Hindt (Nemours Children's Hospital, Wilmington, DE, USA), Pei-Ni Jone (Children's Hospital Colorado, University of Colorado Anschutz Medical Campus - Now affiliated with Lurie Children's Hospital, Northwestern University Feinberg School of Medicine), Hidemi

Kajimoto (Seattle Children's Hospital, Seattle, WA, USA), Kelli Kaneta (Children's Hospital of Los Angeles, Los Angeles, CA, USA), Manaswitha Khare (University of California San Diego/Rady Children's Hospital San Diego, CA USA), Stacie Knutson (University of Minnesota, Minneapolis, MN, USA), Shelby Kutty (Johns Hopkins School of Medicine, Baltimore MD, USA), Lanari M. (Pediatric Emergency Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy), Victoria Maksymiuk (New York Medical College/Maria Fareri Children's Hospital at Westchester Medical Center, Valhalla, NY, USA), Kimberly E. McHugh (Medical University of South Carolina, Charleston, SC, USA), Shae Merves (Arkansas Children's Hospital/University of Arkansas for Medical Sciences, Little Rock, AR, USA), Nilanjana Misra (Cohen Children's Medical Center, Northwell Health, Queens, NY, USA), Sindhu Mohandas (Children's Hospital of Los Angeles, Los Angeles, CA, USA), Tapas Mondal (Division of Cardiology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada), Kambiz Norozi (Department of Pediatrics, Pediatric Cardiology, Western University, London, ON, Canada), Todd Nowlen (Phoenix Children's Hospital, Phoenix, AZ, USA), Joseph J Pagano (Division of Pediatric Cardiology, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada), Deepa Prasad (Banner Children's at Desert Medical Center, Mesa, AZ, USA), Geetha Raghuveer (Children's Mercy Hospital, Kansas City, MO, USA), Prasad Ravi (Banner Children's at Desert Medical Center, Mesa, AZ, USA), Balasubramanian Sundaram (Kanchi Kamakoti Childs Trust Hospital, Chennai, India), Anupam Sehgal (Kingston Health Science Centre, Kingston, ON, Canada), Ashish Shah (Johns Hopkins All Children's Hospital, Saint Petersburg, FL, USA), Belén Toral Vázquez (Hospital 12 de Octubre (Imas12), Madrid, Spain), Adriana H. Tremoulet (University of California San Diego/Rady Children's Hospital San Diego, CA USA), Aishwarya Venkataraman (Kanchi Kamakoti Childs Trust Hospital, Chennai, India), Laurence Watelle (Department of pediatrics, Université de Sherbrooke, and Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke,

QC, Canada), Marco Antonio Yamazaki-Naksahimada (Instituto Nacional de Pediatría,. Mexico City, Mexico), Anji T. Yetman (Children's Hospital and Medical Center. University of Nebraska Medical Center, Omaha NE)

Correspondance: Ashraf S. Harahsheh, Department of Pediatrics, George Washington University School of Medicine & Health Sciences; Division of Cardiology, Children's National Hospital; 111 Michigan Ave, NW Washington, DC 20010, USA. Email: aharahsh@childrensnational.org, Phone 2024762020, Fax 2024765700. ORCID ID: 0000-0002-2622-573X

Total word count of the manuscript: 5000

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 by evidence of prior SARS-CoV-2 infection.

Methods: The International KD Registry (IKDR) enrolled KD and MIS-C patients from sites from North, Central and South America, Europe, Asia and Middle East. Evidence of prior infection was defined as: Positive (+ve household contact or positive 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 89 (4%), Negative 404 (17%) and Unknown for 311 (13%) patients. Clinical outcomes varied significantly between 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, while patients in the Negative and Unknown groups had more severe coronary artery abnormalities.

Conclusion: 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 prior acute SARS CoV2 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.

Key words: Multisystem Inflammatory Syndrome in Children (MIS-C); Kawasaki disease; 2019 novel coronavirus disease (COVID-19) pandemic; coronary artery abnormality; Pediatric Multisystem Inflammatory Syndrome temporally associated with COVID-19 (PIMS)

Abbreviations:

BMI: Body mass index

BNP: B-type natriuretic peptide

BUN: Blood urea nitrogen

CAAs: Coronary artery aneurysms

COVID-19: 2019 novel coronavirus disease

DCC: Data coordinating center

DDU: Di-dimer units

EF: Ejection fraction

GGT: gamma-glutamyl transferase

HS: high sensitivity

ICU: Intensive care unit

IKDR: International Kawasaki disease Registry

IL: Interleukin

IQR: value at the 1st and 3rd percentile

IVIG: Intravenous immunoglobulin

LAD: Left anterior descending coronary artery

LMCA: Left main coronary artery

LOS: length of stay

LVEF: Left ventricular ejection fraction

KD: Kawasaki disease

MIS-C: Multisystem Inflammatory Syndrome in Children

NT-ProBNP: N-terminal B-type natriuretic peptide

NSAIDs: Non-steroidal anti-inflammatory agents

RCA: Right coronary artery

REDCap: Research Electronic Data Capture

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SD: Standard deviation

TNF: Tumor necrosis factor

WBC: White blood cell

Kawasaki disease in the time of COVID-19 and MIS-C – The International Kawasaki Disease Registry

Introduction:

Kawasaki disease (KD), first described in 1967, is characterized by systemic inflammation that may lead to coronary artery aneurysms (CAAs), myocardial ischemia and death.[1] Despite more than 50 years of research, the etiology remains unknown.[2] Thus, 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 it's emergence would facilitate the identification of an underlying etiology for KD.[3-7] Similar to KD, MIS-C is characterized by systemic inflammation[2] and can also be commonly 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 which are in common with other pediatric 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 prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or exposure in the case definition for MIS-C, although outbreaks 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, since prior infection and vaccination may confound the utility of diagnostic testing. We sought to compare demographics, clinical presentation, management, and outcomes of patients by degree of evidence of prior SARS-COV-2 infection. We hypothesized that the level of confidence in the 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.

Material and methods:

International KD Registry:

The International KD 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 beginning in March 2020 and its clinical overlap with KD, prompted the IKDR as of January 2020 to expand data collection to outside North America including 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 either: (1) acute, confirmed, or suspected diagnosis of complete or incomplete KD, or KD shock syndrome with and without CAAs and (2) confirmed or suspected MIS-C.

The IKDR protocols were approved by participating centers with informed consent or waiver of consent depending on the jurisdiction. Depending on jurisdiction and when required, the authors confirm that a patient consent form(s) was obtained for this article. After obtaining legal authorization including data-use agreement, each site submitted deidentified data of their patients to the data coordinating center (DCC) in Toronto, ON, Canada. 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 electrocardiogram, echocardiogram, cardiac MRI, and serial laboratory findings were submitted directly to the DCC for centralized data entry into REDCap. Data quality was ensured by sending verification queries from the DCC to each participating center. Only patients with resolved data queries were included in the analyses. Author BWM 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 (AHA) 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 four groups: **Positive** if the patient had a confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test, either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the 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 this analysis, only the largest z score of any branch at any time was used, and categorized 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), and/or "large or giant aneurysm" (>8 mm in diameter, or z score >10).[22] Ejection fraction (EF) was used to determine left ventricular systolic function. Left ventricular (LV) systolic function was classified as "normal" for LVEF greater than or equal to 55%.[24]

Statistical analysis:

Data are described as frequencies, medians with interquartile range (IQR, value at 1st and 3rd percentile) or means with standard deviation 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 felt to be

normal, then non-parametric 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 using Fisher's exact tests, Chi-square and Mantel-Haentzel Chi-square for categorical variables, Kruskal Wallis analysis of variance for non-normally 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 statistically significant. All analyses were performed using SAS Statistical Software, Version 9.4 (Cary, NC) using default settings.

Results:

Study population. The first MIS-C patient enrolled was hospitalized on March 29, 2020, leading to a total of 1708 patients enrolled by July 18, 2022. Within a similar timeframe (March 29, 2020-July 20, 2022), 637 KD patients were hospitalized. 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 above, the prior SARS-COV-2 infection status was Positive in 1541 (66%) patients, Possible in 89 (4%), Negative in 404 (17%) and Unknown in 311 (13%) patients. 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 males 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 who 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 (IQR) of 4 days (3-6), Possible group 5 (3-7), Negative group 5 (4-7), and Unknown group 5 days (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 to the Negative and Unknown groups; specifically, 64% of Possible and 54% of Possible patients had 2 KD symptoms or less compared to 35% of Negative and 28% of Unknown group patients (Figure 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 mitral valve regurgitation, ≥ small pericardial effusion, and reduced LV function (left ventricular ejection fraction (LVEF) < 55%). (Figure 2) Conversely, patients in the Negative and Unknown groups developed worse CAAs (Z-score ≥ 2.5) (Figure 3) and patients in the Negative group had higher maximum coronary artery z score than all other groups. There were no patients with giant CAA in the positive or possible group.

Clinical outcomes by groups (Table 3). Clinical outcomes varied significantly between the groups, with a greater proportion of patients in the Positive and Possible groups presenting with shock and respiratory dysfunction, admission to the intensive care unit (ICU) and having received respiratory support. The hospital length of stay (LOS) varied significantly between the groups with patients in the

Possible and Positive groups having longer hospital LOS. Death occurred for 6 (0.4%) patients in the Positive group, 3 (3.6%) in the Possible, 2 (0.5%) in the Negative and 1 (0.3%) in the Unknown groups.

Treatment by group (Table 4). Across the groups, 90-97% of patients received at least one dose of intravenous immunoglobulin (IVIG). The proportion of patients who received therapies varied significantly between the groups, with the utilization of heparin, anticoagulants, interleukin (IL) blocker, 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 between groups, with patients in the Positive and Possible groups appearing to have lower albumin, alkaline phosphatase, serum potassium, white blood cell (WBC) count, lymphocytes, macrophages, eosinophils, and platelet count. 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 BNP (NT-ProBNP), and triglycerides. Fibrinogen level differed between 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 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 between 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 ICU admission, longer hospital LOS, and worse cardiac outcomes, including a higher likelihood of cardiac systolic dysfunction, ≥ mild mitral valve regurgitation, and ≥ small pericardial effusion, but not CAAs. Hence, these patients shared similarities with clinical descriptions of MIS-C, versus Unknown and Negative group patients sharing similarities with KD. Differentiating patients based on certainty of SARS-CoV-2 infection/exposure status, thus, is likely a key differentiating factor for diagnosis. These findings support the Centers for Disease Control and Prevention (CDC) decision to preserve SARS-CoV-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 SARS-CoV-2 infection and/or 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 extremities changes varied significantly between the groups, with the patients in the Negative/Unknown groups having higher proportion of patients with these features. (Table 1). Variations of KD features associated with the COVID-19 pandemic has also 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% versus 63% pre-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 body mass index (BMI) z-score and slightly higher triglycerides 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 M et al. found that higher BMI, higher triglycerides and lower high-density lipoprotein (HDL) cholesterol were associated with worse clinical manifestations.[31] Similarly, in this large cohort study of patients, Positive/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. While the long-term cardiac complications in KD have been well described[19,22] the long-term complications 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 categorized by SARS-CoV-2 status in children with MIS-C or KD. Positive/Possible (presumed MIS-C) had a higher likelihood of ventricular dysfunction but less severe CAAs, which is consistent with the findings of other large multicenter MIS-C registries.[39] On a similar note, patients in the Positive/Possible groups appeared to have more severe laboratory findings, consistent with other reports of MIS-C.[33,40]

Intravenous Immunoglobulin (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 as, to our knowledge, there have been no published randomized 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 combination with steroids.[42-46] IKDR and other similar registries are best suited for future nested clinical trials to

355 determine the efficacy of therapies, as well as to use machine learning techniques to personalize therapy
356 and predict response.

357 The strengths of this paper include (1) the inclusion of patients from different parts of the world
358 encompassing both high and low resource countries, and (2) the registry was approved by most centers
359 with waiver of consent which allowed the registry to bypass certain barriers to research, which was
360 reflected in the ethnicity of the population included in the analysis. Most patients in each group were
361 identified as non-white, which corresponds with current real-world experience.[8,39] Finally, (3) the unique
362 combination of validated simultaneous contemporaneous KD and MIS-C patients for comparison in the
363 inclusion of this registry is a further strength.

364 This study should be viewed in light of a number of limitations. Patients were not managed by
365 one standardized protocol and site diagnosis was not adjudicated, and hence there may be differences in
366 clinical practice and reporting across sites and providers. It is also assumed that the sites reported all
367 eligible patients, and the degree to which reporting may have been selective, while unlikely given
368 reporting requirements from sites, is unknown. Another limitation may be caused by underdiagnosing or
369 underreporting of classical KD early in the pandemic, as much as non-availability of PCR testing for
370 SARS-CoV-2 infection in the same period, but this cannot be verified by design of the study. A further
371 limitation is that the Data Coordinating Centre abstracted cardiac findings from submitted reports of
372 echocardiograms, and a centralized core laboratory with a review of submitted recordings was not used.
373 However, studies of the Kawasaki disease population have failed to show substantial differences between
374 local and core laboratory findings, and for clinical purposes, decision-making is based on local findings.[47]
375 In this manuscript, we did not include for each group how often did patients met the 2017 AHA scientific
376 statement KD criteria or the 2020 CDC MIS-C criteria. This is the focus of a future IKDR manuscript
377 along with factors associated with cardiac abnormalities for each condition. Finally, with regard to 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.

Conclusions:

There is an overlap in presentation, management, and early outcomes between SARS CoV2 Positive/Possible (presumed MIS-C) and SARS CoV2 Negative/Unknown (presumed KD) patients and the primary differentiating factor is history of acute SARS CoV2 infection or exposure. SARS CoV2 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. Negative and Unknown cohort (presumed KD) closely corresponded to historical 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.

Acknowledgments: The authors are grateful for Dr. Angela J. Doty for her editorial assistance and for all those who contributed to the success of IKDR including: Somantha Amperayani (Kanchi Kamakoti Childs Trust Hospital, Chennai, India), Jessica Bainton (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), Annette L Baker (Boston Children's Hospital, Harvard Medical School, Boston, MA, USA), Mikayla A. Beckley (Seattle Children's Hospital, Seattle, WA, USA), Bailey Bernknopf (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), Jacobo Borovoy-Gurwitz (Hospital Angeles Lomas, Huixquilucan, Mexico), Jane C. Burns (University of California San

Diego/Rady Children's Hospital San Diego, CA USA), Ana Caro barri (Hospital 12 de Octubre (Imas12), Madrid, Spain), Tanveer Collins (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), Amy Cooper (The Heart Center at Nationwide Children's Hospital, Columbus, OH, USA),

Jamie Cruz (Hospital 12 de Octubre (Imas12), Madrid, Spain), Sarah D de Ferranti (Boston Children's Hospital, Harvard Medical School, Boston, MA, USA), Catherine Dimes (The Heart Center at Nationwide Children's Hospital, Columbus, OH, USA), Elías Duck-Hernández (Hospital Angeles Lomas, Huixquilucan, Mexico), Gulnigor Ganieva (Children's Hospital of Los Angeles, Los Angeles, CA, USA), Guida F. (Pediatric Emergency Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy), Jonathan Hazlewood (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), Ashley Herzberg (Phoenix Children's Hospital, Phoenix, AZ, USA), Katherine Kanwar (The Heart Center at Nationwide Children's Hospital, Columbus, OH, USA), Alicia Kazarians (Children's Hospital of Los Angeles, Los Angeles, CA, USA),

Jong Mi Ko (Johns Hopkins School of Medicine, Baltimore MD, USA), Rita Long (Johns Hopkins School of Medicine, Baltimore MD, USA), Simran Mahanta (Boston Children's Hospital, Harvard Medical School, Boston, MA, USA), Meli M. (Pediatric Emergency Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy), Sahar Mohamed (Kingston Health Science Centre, Kingston, ON, Canada), Deepthi G. Nair (Seattle Children's Hospital, Seattle, WA, USA), Jane W Newburger (Boston Children's Hospital, Harvard Medical School, Boston, MA, USA), Martin Ogwuru (Kingston Health Science Centre, Kingston, ON, Canada), Sunita O'Shea (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), Susan S. Park (Phoenix Children's Hospital, Phoenix, AZ, USA), Jade Porche (Phoenix Children's Hospital, Phoenix, AZ, USA), Sulochana pultilibai (Kanchi Kamakoti Childs Trust Hospital, Chennai, India), Irene Maulen

Radovan (Hospital Angeles Lomas, Huixquilucan, Mexico), Itzel Estefani Ríos-Olivares (Instituto Nacional de Pediatría,. Mexico City, Mexico), Martha Rolland (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), Christina Hayden Rush (Children's Hospital of Philadelphia, Philadelphia, PA, USA), Kristy Rutt (Banner Children's at Desert Medical Center, Mesa, AZ, USA), Senthilnathan . S (Kanchi Kamakoti Childs Trust Hospital, Chennai, India), Gurudess S. (Kanchi Kamakoti Childs Trust Hospital, Chennai, India), Seaher Sakha (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada), John Smythe (Kingston Health Science Centre, Kingston, ON, Canada), Samantha Stack (Phoenix Children's Hospital, Phoenix, AZ, USA), Robert W. Lowndes (Children's National Hospital, George Washington University School of Medicine, Washington, DC, USA), Patricia Walter (Labatt Family Heart Centre, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada).

Funding and financial interest: Dr. Harahsheh is supported by a Sub-agreement from the Johns Hopkins University with funds provided by Grant No. R61HD105591 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development and the Office of the Director, National Institute of Health (OD). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development, the Office of the Director, National Institute of Health (OD), the National Institute of Health, the NIBIB, the NHLBI, or the Johns Hopkins University.

Non-financial interest: Dr. Harahsheh serves as a scientific advisory board member of OP2 DRUGS ("OP2"). This advisory position has no relevant disclosures for this manuscript.

Disclosures/ Conflict of interest: None

Ethics approval: The International KD Registry (IKDR) protocols were approved by participating centers with informed consent or waiver of consent depending on jurisdiction. Depending on jurisdiction and when required, the authors confirm that a patient consent form(s) was obtained for this article.

Availability of data and material: Data will be available upon a reasonable request.

Author contributions: Ashraf S. Harahsheh was involved in study design, analysis of data, and drafting the manuscript. Samay Shah was involved in drafting the tables and revising the manuscript. Brian W. McCrindle was involved in study design, analysis of data, creating the figures, and revising the manuscript. All other authors were involved in collecting data, interpretation of the data and revising the manuscript. All authors approved the final version to be published.

References:

1. Kawasaki T. [Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children]. *Arerugi*. Mar 1967;16(3):178-222.

2. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease? *Trends Cardiovasc Med*. Oct 2020;30(7):389-396. doi:10.1016/j.tcm.2020.07.004

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*. Apr 1 2021;4(4):e214475. doi:10.1001/jamanetworkopen.2021.4475

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*. Nov 2020;2(6):632-640. doi:10.1016/j.cjco.2020.09.004

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*. Jan 1 2022;41(1):e21-e25. doi:10.1097/INF.0000000000003388

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*. Jun 8 2020;doi:10.1001/jama.2020.10369

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*. Oct 2021;37(10):1619-1628. doi:10.1016/j.cjca.2021.05.014

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*. Aug 5 2021:1-9. doi:10.1017/S1047951121003024

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*. Oct 22 2021:1-11. doi:10.1007/s40124-021-00258-5

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*. Jan 7 2023;doi:10.1016/j.cjca.2023.01.002

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*. May 16 2022;13(1):2687. doi:10.1038/s41467-022-30357-w

12. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) https://emergency.cdc.gov/han/2020/han00432.asp. Accessed on 5/16/2020.

13. Multisystem inflammatory syndrome in children and adolescents with COVID-19. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed on 5/16/2020.

14. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatricmultisystem-%20inflammatory%20syndrome-20200501.pd. Accessed on 5/10/2020.

15. 2023 CDC Multisystem Inflammatory Syndrome in Children (MIS-C) case defintion https://www.cdc.gov/mis/mis-c/hcp_cstecdc/index.html Accessed on 01-30-2023.

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*. Feb 15 2005;191(4):499-502. doi:10.1086/428291

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*. Jul 16 2021;11(1):14617. doi:10.1038/s41598-021-93089-9

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*. Oct 2020;36(10):1598-1607. doi:10.1016/j.cjca.2020.01.016

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*. Aug 4 2020;9(15):e016440. doi:10.1161/JAHA.119.016440

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*. Mar 2021;42(3):676-684. doi:10.1007/s00246-020-02529-2

21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. Apr 2009;42(2):377-81. doi:10.1016/j.jbi.2008.08.010

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*. Apr 25 2017;135(17):e927-e999. doi:10.1161/CIR.0000000000000484

524 23. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki
525 disease: risk factors from analysis of serial normalized measurements. *Circulation*. Jul 10
526 2007;116(2):174-9. doi:10.1161/CIRCULATIONAHA.107.690875
527 24. Margossian R, Schwartz ML, Prakash A, et al. Comparison of echocardiographic and cardiac
528 magnetic resonance imaging measurements of functional single ventricular volumes, mass, and ejection
529 fraction (from the Pediatric Heart Network Fontan Cross-Sectional Study). *Am J Cardiol*. Aug 1
530 2009;104(3):419-28. doi:10.1016/j.amjcard.2009.03.058
531 25. Son MBF, Burns JC, Newburger JW. A New Definition for Multisystem Inflammatory Syndrome
532 in Children. *Pediatrics*. Mar 1 2023;151(3)doi:10.1542/peds.2022-060302
533 26. Toubiana J, Cohen JF, Brice J, et al. Distinctive Features of Kawasaki Disease Following SARS-
534 CoV-2 Infection: a Controlled Study in Paris, France. *J Clin Immunol*. Apr 2021;41(3):526-535.
535 doi:10.1007/s10875-020-00941-0
536 27. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the
537 Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. Jun 6
538 2020;395(10239):1771-1778. doi:10.1016/S0140-6736(20)31103-X
539 28. Fernandez-Cooke E, Grasa CD, Dominguez-Rodriguez S, et al. Prevalence and Clinical
540 Characteristics of SARS-CoV-2 Confirmed and Negative Kawasaki Disease Patients During the
541 Pandemic in Spain. *Front Pediatr*. 2020;8:617039. doi:10.3389/fped.2020.617039
542 29. Burney JA, Roberts SC, DeHaan LL, et al. Epidemiological and Clinical Features of Kawasaki
543 Disease During the COVID-19 Pandemic in the United States. *JAMA Netw Open*. Jun 1
544 2022;5(6):e2217436. doi:10.1001/jamanetworkopen.2022.17436

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*. May 22 2020;369:m1985. doi:10.1136/bmj.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. doi:10.3389/fcvm.2022.1033660

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*. Aug 4 2020;142(5):429-436. doi:10.1161/CIRCULATIONAHA.120.048360

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*. Jun 7 2021;doi:10.1016/j.jpeds.2021.06.002

34. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem Inflammatory Syndrome in Children in New York State. *N Engl J Med*. Jun 29 2020;doi:10.1056/NEJMoa2021756

35. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *N Engl J Med*. Jun 29 2020;doi:10.1056/NEJMoa2021680

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*. Oct 27 2020;76(17):1947-1961. doi:10.1016/j.jacc.2020.08.056

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*. Dec 30 2021;23(1):140. doi:10.1186/s12968-021-00841-1

38. Alsaied T, Tremoulet AH, Burns JC, et al. Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children. *Circulation*. Jan 5 2021;143(1):78-88. doi:10.1161/CIRCULATIONAHA.120.049836

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*. Aug 1 2021;175(8):837-845. doi:10.1001/jamapediatrics.2021.0630

40. Fridman MD, Tsoukas P, Jeewa A, Yeung RSM, Gamulka BD, McCrindle BW. Differentiation of COVID-19-Associated Multisystem Inflammatory Syndrome From Kawasaki Disease With the Use of Cardiac Biomarkers. *Can J Cardiol*. Dec 1 2022;doi:10.1016/j.cjca.2022.11.012

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*. Feb 14 2023;doi:10.1016/S2665-9913(23)00029-2

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*. Nov 29 2022;doi:10.1016/j.cjca.2022.11.011

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*. Apr 2022;74(4):e1-e20. doi:10.1002/art.42062

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. doi:10.3389/fped.2021.667507

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*. Feb 2021;5(2):133-141. doi:10.1016/S2352-4642(20)30304-7

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*. Feb 8 2021;47(1):24. doi:10.1186/s13052-021-00980-2

47. Margossian R, Lu M, Minich LL, et al. Predictors of coronary artery visualization in Kawasaki disease. *J Am Soc Echocardiogr*. Jan 2011;24(1):53-9. doi:10.1016/j.echo.2010.10.015

603 **Table 1. Demographics and symptoms stratified by patient groups.**

Item	Sub-items	Positive 1541 (66%)	Possible 89 (4%)	Negative 404 (17%)	Unknown 311 (13%)	p value
Sex (Male) n (%)		954 (62%)	48 (54%)	244 (60%)	184 (59%)	0.41
Median (IQR) age at admission (years)		8 (5-12)	7.6 (4-11)	3 (1-7)	3 (1-5.5)	<0.001
Race/Ethnicity n (%)		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 people	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 (mean ± SD)		N=1483	N=82	N=374	N=289	<.0001
		0.60±1.40	0.36±1.29	0.12±1.34	-0.11±1.43	
Median (IQR) duration of symptoms before admission (days)		N=1473	N=87	N=396	N=305	<.0001
		4 (3-6)	5 (3-7)	5 (4-7)	5 (3-6)	
Total duration of fever (days) median (IQR)		N=1496	N=85	N=393	N=305	<.0001
		6 (5-8)	7 (5-10)	7 (5-10)	7 (5-10)	
Conjunctivitis n (%)		930 (60%)	56 (63%)	260 (64%)	237 (76%)	<.0001
Cervical lymphadenopathy n (%)		365 (24%)	27 (30%)	145 (36%)	103 (33%)	<.0001
Extremity changes n (%)		390 (25%)	27 (30%)	207 (51%)	181 (58%)	<.0001
Skin rash n (%)		853 (55%)	52 (58%)	300 (74%)	244 (78%)	<.0001
Oral mucosal changes n (%)		510 (33%)	40 (45%)	237 (59%)	199 (64%)	<.0001
Number of Kawasaki disease (KD) clinical criteria n (%)	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 (%)		N=1539	N=89	N=404	N=311	0.17
		387 (25%)	30 (34%)	117 (29%)	81 (26%)	
Sore throat n (%)		N=1538	N=89	N=403	N=311	<.0001
		370 (24%)	28 (31%)	66 (16%)	48 (15%)	
Abdominal Pain n (%)		N=1539	N=89	N=404	N=311	<.0001
		990 (64%)	52 (58%)	126 (31%)	73 (23%)	
Diarrhea n (%)		N=1540	N=89	N=404	N=311	<.0001

	737 (48%)	37 (42%)	129 (32%)	94 (30%)	
Vomiting n (%)	958 (62%)	58 (65%)	180 (45%)	120 (39%)	<.0001
Anorexia n (%)	N=1514	N=87	N=395	N=307	0.002
	390 (26%)	20 (23%)	68 (17%)	62 (20%)	
Arthritis n (%)	N=1539	N=89	N=403	N=311	0.02
	59 (4%)	2 (2%)	28 (7%)	12 (4%)	
Myalgias n (%)	N=1541	N=89	N=403	N=311	<.0001
	388 (25%)	10 (11%)	40 (10%)	21 (7%)	
Dyspnea n (%)	N=1538	N=89	N=402	N=310	<.0001
	263 (17%)	10 (11%)	20 (5%)	11 (4%)	
Headache n (%)	N=1537	N=89	N=401	N=310	<.0001
	567 (37%)	21 (24%)	65 (16%)	33 (11%)	
Irritability n (%)	N=1514	N=87	N=395	N=307	<.0001
	247 (16%)	17 (20%)	118 (30%)	110 (36%)	
Hepatomegaly n (%)	N=1514	N=87	N=396	N=307	0.14
	72 (4%)	2 (2%)	10 (3%)	10 (3%)	

Abbreviations: BMI: Body mass index. IQR: value at the 1st and 3rd percentile, KD, Kawasaki disease, SD: Standard deviation. Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test, either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not performed.

Table 2. Echocardiogram findings stratified by patient group

Item	Sub-items	Positive N=1541 (66%)	Possible N=89 (4%)	Negative N=404 (17%)	Unknown N=311 (13%)	p value
Maximum RCA z score (continuous variable) median (IQR)		N=1324	N=67	N=368	N=246	0.0006
		0.77 (-0.03-1.54)	0.84 (0.15-1.76)	1.02 (0.4-1.7)	0.76 (0.02-1.5)	
Maximum LMCA z score (continuous variable) median (IQR)		N=1275	N=66	N=366	N=246	0.36
		0.61 (-0.13-1.33)	0.52 (0.07-1.08)	0.83 (0.16-1.57)	0.47 (-0.30-1.26)	
Maximum LAD z score (continuous variable) median (IQR)		N=1246	N=66	N=363	N=220	0.14
		0.78 (-0.03-1.51)	0.59 (-0.05-1.19)	0.56 (0.01-1.29)	0.61 (-0.11-1.6)	
Maximum Circumflex coronary artery z score (continuous variable) median (IQR)		N=803	N=48	N=283	N=171	0.07
		-0.57 (-1.48-0.34)	-0.17 (-1.27-0.39)	-0.47 (-1.33-0.51)	-0.28 (-1.20-0.53)	
Maximum coronary artery z score in any branch at any timepoint		N=1485	N=82	N=398	N=265	0.02
		1.18 (0.33-1.86)	0.95 (0.00-1.76)	1.34 (0.68-1.91)	1.16 (0.36-1.99)	
Degree of ventricular dysfunction n (%)		N=1300	N=75	N=354	N=204	<0.0001
	EF ≥55%	808 (62%)	57 (76%)	323 (91%)	171 (84%)	
	EF 40-54%	406 (31%)	15 (20%)	25 (7%)	31 (15%)	
	EF ≤40%	86 (7%)	3 (4%)	6 (2%)	2 (1%)	
LVEF (%) (continuous variable) median (IQR)		N=1300	N=75	N=354	N=204	<0.0001
		57 (50.4-62)	59.6 (55.8-63)	62 (59-65.8)	63 (58.4-67.35)	
Mitral valve regurgitation grade n (%)		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 (%)		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%)	

Abbreviations: CAA: Coronary artery aneurysm, EF: Ejection fraction, IQR: value at the 1st and 3rd percentile, LAD: Left anterior descending coronary artery, LMCA: Left main coronary artery, LVEF: Left ventricular ejection fraction, RCA: Right coronary artery, SD: Standard deviation. Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test, either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features

of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not performed

Table 3. Clinical Outcomes stratified by patient group

Item	Sub-items	Positive N=1541 (66%)	Possible N=89 (4%)	Negative N=404 (17%)	Unknown N=311 (13%)	p value
Admitted to ICU n (%)		N=1538	N=89	N=404	N=311	<.0001
		844 (55%)	37 (42%)	55 (14%)	49 (16%)	
Shock n (%)		N=1537	N=89	N=402	N=309	<.0001
		498 (32%)	29 (33%)	25 (6%)	14 (5%)	
Cardiac arrest/failure n (%)		N=1535	N=89	N=403	N=311	0.04
		40 (3%)	3 (3%)	5 (1%)	2 (0.6%)	
Arrhythmia n (%)		N=1535	N=89	N=402	N=310	0.0003
		112 (7%)	7 (8%)	12 (3%)	9 (3%)	
Respiratory support n (%)		N=1537	N=89	N=402	N=302	<0.0001
		568 (37%)	21 (24%)	42 (10%)	19 (6%)	
Respiratory dysfunction* n (%)		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 (%)		N=1534	N=89	N=403	N=311	<0.0001
		132 (9%)	2 (2%)	11 (3%)	1 (0.3%)	
Total hospital length of stay (days) median (IQR)		7 (5-10)	6 (4-8)	5 (4-8)	5 (4-8)	<.0001
Total duration of initial ICU stay (days) median (IQR)		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 (%)		N=1526	N=88	N=403	N=310	<.0001
		57 (3.74%)	7 (7.95%)	26 (6.45%)	32 (10.32%)	

Abbreviations: ICU: Intensive care unit, IQR: value at the 1st and 3rd percentile. Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test, either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not performed

*Respiratory dysfunction was defined as None if O2 saturation was >93% on room air, no dyspnea nor abnormal CXR, moderate if there was tachypnea, +/- hypoxia O2 sat ≤ 93% on room air and abnormal chest imaging with less than 50% involvement of the lung parenchyma, and severe if there was

tachypnea, with hypoxia O2 saturation ≤ 93 percent on room air or PaO2/FiO2 < 300 mmHg and more than 50% involvement of the lung parenchyma on chest imaging

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

730 **Table 4. Treatments stratified by patient group**

Item	Sub-items	Positive 1541 (66%)	Possible 89 (4%)	Negative 404 (17%)	Unknown 311 (13%)	p value
Number of IVIG doses n (%)		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 (%)		N=1448	N=84	N=363	N=301	0.40
		174 (12%)	8 (10%)	53 (15%)	42 (14%)	
Number of days between hospital admission and first IVIG median (IQR)		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 (%)		N=1539	N=89	N=403	N=310	<.0001
		1182 (77%)	57 (64%)	151 (37%)	93 (30%)	
Oral steroids n (%)		N=1533	N=89	N=404	N=311	<.0001
		927 (60%)	41 (46%)	147 (36%)	86 (28%)	
TNF-alpha inhibitor (ex. Infliximab, Etanercept) n (%)		N=1538	N=89	N=404	N=311	0.30
		88 (6%)	1 (1%)	24 (6%)	16 (5%)	
IL-1-blocker (ex. Anakinra) n (%)		N=1539	N=89	N=404	N=311	<.0001
		277 (18%)	9 (10%)	22 (5%)	15 (5%)	
Antiplatelet therapy n (%)		N=1541	N=89	N=404	N=310	<.0001
		1228 (80%)	67 (75%)	353 (87%)	287 (93%)	
Unfractionated heparin n (%)		N=1539	N=89	N=404	N=310	<.0001
		177 (12%)	10 (11%)	9 (2%)	2 (1%)	
Anticoagulants n (%)		N=1540	N=89	N=404	N=311	<.0001
		795 (52%)	25 (28%)	71 (18%)	33 (11%)	
Direct oral anticoagulant n (%)		N=1529	N=89	N=403	N=310	<.0001
		103 (7%)	2 (2%)	6 (1%)	0	
NSAIDs n (%)		N=1536	N=89	N=402	N=309	<.0001
		572 (37%)	28 (31%)	110 (27%)	72 (23%)	
Inotropes n (%)		N=1540	N=89	N=404	N=311	<.0001
		647 (41%)	26 (29%)	81 (20%)	27 (9%)	
Diuretics n (%)		211(14%)	5 (6%)	11(3%)	8 (3%)	<.0001
Antivirals n (%)		N=1538	N=89	N=404	N=311	0.0001
		47 (3%)	1 (1%)	1 (0.3%)	0	
Antibiotics n (%)		459 (30%)	13 (15%)	77 (19%)	56 (18%)	<0.0001

731 **Abbreviations**: IL: Interleukin, IQR: value at the 1st and 3rd percentile, IVIG: intravenous

732 immunoglobulin, NSAIDs: Non-steroidal anti-inflammatory agents, TNF: Tumor necrosis factor. Patients

733 were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a confirmed

household contact within the 4 weeks prior to the onset of symptoms and/or positive test, either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not performed

775 **Table 5. Median (IQR) 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	N=69	N=336	N=209	<0.0001
	32 (27-37)	31 (27-36)	34 (29-38)	34 (30-39)	
Alkaline phosphatase (U/L)	N=1124	N=46	N=205	N=174	<0.0001
	141 (108-187.5)	149 (111-187)	173 (138-225)	180 (141-227)	
Alanine transferase (U/L)	N=1188	N=55	N=243	N=191	0.15
	39 (27-62)	33 (25-54)	41 (29-64)	35 (26-60)	
Aspartate transaminase (U/L)	N=1236	N=69	N=293	N=222	0.11
	31 (19-53)	22 (14-55)	27 (17-60)	25.5 (15-71)	
GGT (U/L)	N=332	N=26	N=111	N=88	0.06
	34.5 (21-71.5)	37 (20-64)	28 (14-63)	38 (15.5-85)	
Total bilirubin (umol/L)	N=1234	N=65	N=225	N=194	<0.0001
	9.85 (6.84-15.39)	7.90 (5.13-11.97)	7.70 (5.13-10.26)	6.84 (5.13-10.26)	
Direct bilirubin (umol/L)	N=589	N=46	N=126	N=100	0.005
	3.42 (1.71-6.84)	3.42 (2.40-5.00)	3.00 (1.40-5.13)	3.42 (1.71-3.42)	
Amylase (U/L)	N=1421	N=4	N=16	N=20	0.69
	54.00 (33.00-76.50)	51.00 (25.50-83.50)	54.50 (37.50-86.00)	44.50 (41.00-64.50)	
Blood urea nitrogen (BUN) (mmol/L)	N=1230	N=57	N=223	N=168	<0.0001
	4.28 (3.21-6.43)	3.93 (2.86-5.00)	3.21 (2.50-4.28)	3.59 (2.50-5.36)	
Creatinine (umol/L)	N=1281	N=72	N=268	N=202	<0.0001
	45.08 (33.6-61.88)	43.50 (32.86-61.89)	30.94 (22.54-41.56)	27.20 (20.34-38.01)	
Sodium [NA] (mmol/L)	N=1322	N=74	N=363	N=230	<.0001
	134 (132-137)	135 (133-138)	136 (134-138)	135 (133-137)	
Chloride (mmol/L)	N=1256	N=69	N=304	N=208	0.0003
	101.5 (98-105)	100 (98-105)	103 (100-105)	102 (99-105)	
Potassium [K] (mmol/L)	N=1309	N=74	N=356	N=214	<0.0001
	3.9 (3.5-4.3)	3.95 (3.5-4.2)	4.3 (3.9-4.8)	4.2 (3.8-4.7)	
Bicarbonate (mmol/L)	N=896	N=32	N=153	N=156	0.27
	21 (19-24)	21 (18.6-23)	22 (20-24)	21 (19-24)	
Erythrocyte sedimentation rate (ESR) (mm/hr)	N=869	N=50	N=203	N=148	0.005
	46 (30-70)	50.5 (33-60)	51 (30-73)	60 (33.5-83.5)	
C-reactive protein (mg/L)	N=1187	N=64	N=223	N=222	<0.0001
	140 (71-213.9)	122.18 (59.5-211.45)	83.5 (41-156.5)	86.6 (41.2-151)	
D-dimer (ug/mL DDU)	N=1246	N=60	N=238	N=144	<0.0001
	1.44 (0.83-2.13)	1.00 (0.53-1.79)	0.84 (0.47-1.81)	0.86 (0.46-1.62)	
Ferritin (ug/L)	N=1260	N=70	N=290	N=156	<.0001
	385.5 (212.65-733.45)	283.25 (167.4-602.6)	183.5 (115.6-333.9)	184.5 (101.5-302.5)	

Fibrinogen (g/L)	N=986	N=56	N=226	N=124	0.0005
	5.2 (4.19-6.33)	5.1 (4.28-6.33)	4.8 (3.3-6.2)	5.5 (4.54-6.8)	
Procalcitonin (ug/L)	N=422	N=15	N=34	N=46	<0.0001
	4.04 (1.55-13.21)	1.6 (0.2-8)	1.03 (0.44-3.5)	1.34 (0.6-3.5)	
Lactate dehydrogenase (U/L)	N=1002	N=52	N=176	N=125	0.002
	363 (269-605)	271.5 (231-467.5)	426.5 (288-665)	374 (266-559)	
BNP (ng/L)	N=463	N=19	N=43	N=65	0.02
	176 (32.6-564)	288 (58-729)	118 (14-395)	104 (36-234)	
NT-ProBNP (ng/L)	N=526	N=43	N=120	N=60	<.0001
	2349 (479-8600)	855 (452-3378)	321.2 (129.5-1249)	649.5 (255.5-3047.5)	
HS Troponin I (ng/L)	N=111	N=17	N=25	N=22	0.002
	34 (9.99-140)	39 (16-78)	14.00 (4-25)	7.50 (4.72-21)	
Troponin I (ng/L)*	N=712	N=34	N=138	N=95	<0.0001
	15 (5.35-80.9)	10.65 (2.7-61)	9.99 (9.99-11.4)	10 (4.5-17)	
Red blood cells (RBC) count (x10^12/L)	N=1299	N=69	N=386	N=246	0.46
	4.14 (3.75-4.52)	4.11 (3.87-4.49)	4.17 (3.79-4.5)	3.14 (3.76-4.39)	
Hemoglobin (g/L)	N=1371	N=74	N=388	N=246	0.002
	113 (102-124)	110 (102-120)	110 (101-120)	109 (100-119)	
White blood cell (WBC) count (x10^9/L)	N=1260	N=79	N=389	N=247	<.0001
	9.70 (6.9-13.7)	10.3 (7.7-15.3)	12.3 (8.7-17.36)	13.02 (9.2-17.2)	
Neutrophils (x10^9/L)	N=1226	N=74	N=353	N=189	0.29
	7.20 (4.7-10.69)	7.57 (4.5-12.92)	7.43 (4.2-10.7)	8 (5.04-11.6)	
Lymphocytes (x10^9/L)	N=1175	N=73	N=349	N=184	<0.0001
	1.11 (0.65-1.93)	1.36 (0.8-2.4)	2.81 (1.42-4.7)	2.6 (1.4-4.12)	
Macrophages (x10^9/L)	N=1124	N=65	N=340	N=173	<.0001
	0.38 (0.2-0.64)	0.5 (0.2-0.83)	0.75 (0.4-1.2)	0.7 (0.4-1.11)	
Eosinophils (x10^9/L)	N=995	N=65	N=218	N=160	<.0001
	0.1 (0.01-0.22)	0.1 (0-0.22)	0.15 (0.02-0.42)	0.19 (0.02-0.4)	
Basophils (x10^9/L)	N=970	N=60	N=287	N=147	<.0001
	0.01 (0-0.03)	0 (0-0.02)	0.03 (0-0.08)	0.01 (0-0.06)	
Platelet count (x10^9/L)	N=1168	N=75	N=325	N=240	<.0001
	180 (126-263)	242 (134-332)	323 (213-424)	347 (238-465)	
Prothrombin time (sec)	N=825	N=49	N=118	N=113	<.0001
	14.9 (13.8-16.2)	14.7 (14-15.9)	14.1 (13-15.1)	14.1 (13.3-15.2)	
Partial thromboplastin time (sec)	N=850	N=55	N=148	N=114	<.0001
	33 (29.7-37.3)	33.3 (30.9-38.5)	31 (27.15-35)	31.4 (28-35)	
INR	N=837	N=53	N=142	N=110	<.0001
	1.20 (1.10-1.34)	1.17 (1.02-1.34)	1.13 (1.07-1.20)	1.20 (1.08-1.3)	
Triglycerides (umol/L)	N=477	N=35	N=167	N=48	0.04
	1.82 (1.29-2.6)	1.84 (1.11-2.31)	1.62 (1.16-2.19)	1.52 (1.12-1.89)	

Abbreviations: BNP: B-type natriuretic peptide, DDU: Di-dimer units, GGT: gamma-glutamyl transferase, HS: high sensitivity, IL: Interleukin, INR: International normalization ratio, IQR: value at the 1st and 3rd percentile, NT: N-terminal,

779 *for patients with Troponin I values reported < 10 (below the detectable range) a value of 9.99 was
780 arbitrarily entered.
781 Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a
782 confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test,
783 either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical
784 features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR
785 or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative
786 serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not
787 performed
788
789 **Figure Legends:**
790 **Figure 1: Number of Kawasaki Disease Clinical Features by SARS-CoV-2 Status**
791 **Abbreviations**: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
792 Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a
793 confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test,
794 either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical
795 features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR
796 or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative
797 serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not
798 performed.
799 **Figure 2: Lowest Left Ventricular Ejection Fraction (%) by SARS-CoV-2 Status**
800 **Abbreviations**: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, LV: Left ventricle
801 Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a
802 confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test,

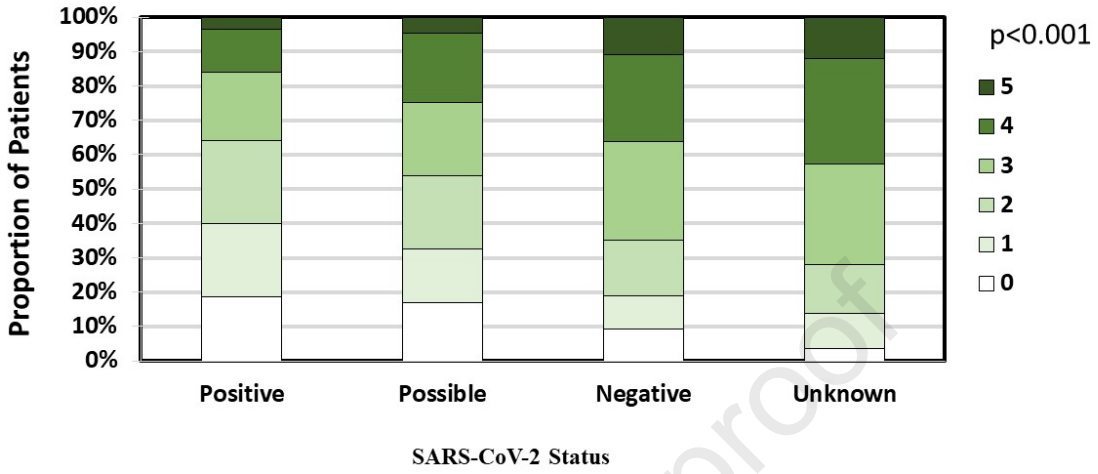
either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not performed.

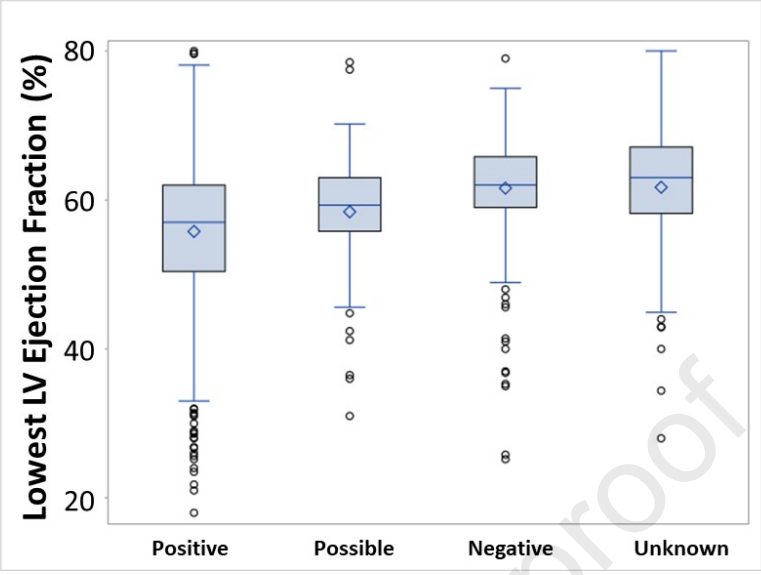
Figure 3: Coronary Artery z-Score Category by SARS-CoV-2 Status

Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

The largest z score of any branch at any time was used, and categorized 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), and/or "large aneurysm" (>8 mm in diameter, or zscore >10).[22]

Patients were stratified by SARS-CoV-2 infection status into four groups: **Positive** if the patient had a confirmed household contact within the 4 weeks prior to the onset of symptoms and/or positive test, either polymerase chain reaction (PCR), serology or both, **Possible** if the patient had suggestive clinical features of MIS-C and/or KD with absent household contact but with only one negative test, either PCR or serology but not both, **Negative** if the patient had no exposure and had negative PCR and negative serology, and **Unknown** if the patient had no known exposure and the PCR and serology testing were not performed.





p<0.0001