CORRESPONDENCE

SARS-CoV-2 Variants and Multisystem Inflammatory Syndrome in Children

TO THE EDITOR: Multisystem inflammatory syndrome in children (MIS-C), a delayed hyperinflammatory response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is an important cause of illness in children. Changes in the prevalent variant throughout the coronavirus disease 2019 pandemic have influenced the transmissibility and incidence of disease, but their association with clinical presentation and outcomes of MIS-C is incompletely known.[1,2]

We used data from the International Kawasaki Disease Registry (IKDR) to identify patients who had been hospitalized with SARS-CoV-2 infection during the period from April 2020 through June 2022 and met the criteria for MIS-C according to the Centers for Disease Control and Prevention. All eligible patients who had provided written informed consent or assent with parental consent, as applicable according to local regulations, were enrolled in the study at the participating sites. Patients were enrolled retrospectively if they had been hospitalized before local approval of the study was obtained and prospectively thereafter. The Global Initiative on Sharing All Influenza Data (GISAID) database of hCoV-19 sequences was used to stratify the patients according to periods defined according to the predominant locally circulating ancestral or variant lineages in order to determine associations with changes in patient and disease characteristics.[3,4] All comparisons were made against the ancestral period, and the 95% confidence intervals for the differences have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

A total of 2017 patients were enrolled in the study. The demographic characteristics of the patients (Table S1 in the Supplementary Appendix, available with the full text of the letter at NEJM.org) were similar to those of the broader population of children with MIS-C. Patients during the delta (B.1.617.2) and omicron (B.1.1.529) periods were younger, showed greater phenotypic similarity to patients with Kawasaki's disease, and had a lower incidence of respiratory dysfunction and coronary-artery dilatation than patients during the ancestral and alpha+ (B.1.1.7 plus other circulating minor variants) periods (Table 1). After the ancestral period, immunomodulatory management evolved to include greater use of glucocorticoids. Concurrently, the risks of serious complications (arrhythmia, cardiac arrest, renal complications, coagulopathy, and thrombosis), admission to an intensive care unit, and death decreased, with the most pronounced decrease occurring during the omicron period. Across all the variant periods, the risk of ventricular dysfunction was highest among the patients hospitalized during the alpha+ period as compared with those during the ancestral period (35% vs. 28%, relative risk, 1.19; 95% confidence interval, 1.04 to 1.35). Although the clinical phenotype became milder over time, severe disease was still prevalent, with 23% of the patients during the omicron period presenting with shock and with 37% being admitted to an intensive care unit.

The features of MIS-C at presentation were more often similar to the features of Kawasaki's disease among patients hospitalized with SARS-CoV-2 infection during the more recent variant periods than among those during the earlier periods; however, without a definitive diagnostic test for either condition, it remains to be determined whether this represents a true change in phenotype or an increase in the number of patients with Kawasaki's disease who meet the criteria for MIS-C through concurrent but unrelated SARS-CoV-2 infection. Although we acknowledge the limitations of the ecologic study design and the inherent risk of misclassification of variant at the patient level, our data support observations that the severity of MIS-C has decreased with each sub-

Table 1. Characteristics of Patients Hospitalized with SARS-CoV-2 Infection Who Received a Diagnosis of MIS-C during Each of the Ancestral and Variant Periods.*

Characteristic	Ancestral Period (N = 710)	Alpha+ Period (N = 748)	Delta Period (N = 319)	Omicron Period (N = 240)	Difference (95% CI)†		
					Alpha+ vs. Ancestral	Delta vs. Ancestral	Omicron vs. Ancestral
Demographic information							
Age — yr	7.5±5.1	8.7±5.2	7.4±4.6	7.2±4.5	1.19 (0.67 to 1.70)	−0.11 (−0.77 to 0.54)	−0.31 (−1.04 to 0.42)
Male sex — no. (%)	417 (58.7)	453 (60.6)	204 (63.9)	153 (63.8)	1.04 (0.94 to 1.16)	1.17 (0.96 to 1.42)	1.17 (0.93 to 1.49)
Presentation and outcomes — no./total no. (%)							
Kawasaki's disease with all diagnostic criteria met	128/708 (18.1)	103/744 (13.8)	66/316 (20.9)	68/240 (28.3)	0.86 (0.73 to 1.00)	1.13 (0.89 to 1.41)	1.52 (1.18 to 1.92)
Respiratory dysfunction	247/705 (35.0)	260/745 (34.9)	85/318 (26.7)	56/239 (23.4)	1.00 (0.89 to 1.11)	0.76 (0.61 to 0.94)	0.65 (0.49 to 0.85)
Coronary-artery dilatation — no./total no. (%)‡	137/692 (19.8)	159/716 (22.2)	49/307 (16.0)	34/229 (14.8)	1.07 (0.94 to 1.21)	0.83 (0.63 to 1.08)	0.77 (0.54 to 1.06)
Shock	196/706 (27.8)	206/746 (27.6)	74/319 (23.2)	55/239 (23.0)	1.00 (0.89 to 1.12)	0.85 (0.67 to 1.06)	0.83 (0.62 to 1.08)
Patient care — no./total no. (%)							
Intravenous glucocorticoids	411/709 (58.0)	523/746 (70.1)	222/319 (69.6)	162/240 (67.5)	1.31 (1.17 to 1.47)	1.43 (1.16 to 1.77)	1.36 (1.07 to 1.75)
ICU admission	336/710 (47.3)	366/748 (48.9)	137/319 (42.9)	89/239 (37.2)	1.03 (0.93 to 1.14)	0.89 (0.73 to 1.07)	0.73 (0.58 to 0.93)

* Plus–minus values are means ±SD. Alpha+ is the B.1.1.7 variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plus other minor circulating variants during the period, delta is the B.1.617.2 variant, and omicron is the B.1.617.2 variant. ICU denotes intensive care unit, and MIS-C multisystem inflammatory syndrome in children.
† Differences are shown as relative risks, except for the differences in age, which are shown as point estimates (differences in mean values). Each variant period was compared with the ancestral period to calculate the difference. The widths of the 95% confidence intervals (CIs) have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
‡ Coronary-artery dilatation was defined as a maximum z score for the coronary-artery diameter of 2 to less than 5 during hospitalization.

sequent SARS-CoV-2 variant. Nevertheless, critical illness in patients hospitalized with MIS-C remains prevalent.

Brian W. McCrindle, M.D., M.P.H.
Hospital for Sick Children
Toronto, ON, Canada

Ashraf S. Harahsheh, M.D.
Children's National Hospital
Washington, D.C.

Ryan Handoko, M.D.
Blalock-Taussig-Thomas Congenital Heart Center at Johns Hopkins University
Baltimore, MD

Geetha Raghuveer, M.D.
Children's Mercy Hospital
Kansas City, MO

Michael A. Portman, M.D.
Seattle Children's Research Institute
Seattle, WA

Michael Khoury, M.D.
Stollery Children's Hospital
Edmonton, AB, Canada

Jane W. Newburger, M.D., M.P.H.
Boston Children's Hospital
Boston, MA

Simon Lee, M.D.
Nationwide Children's Hospital
Columbus, OH

Supriya S. Jain, M.D.
Maria Fareri Children's Hospital at Westchester Medical Center
Valhalla, NY

Manaswitha Khare, M.D.
Rady Children's Hospital
San Diego, CA

Nagib Dahdah, M.D.
Centre Hospitalier Universitaire Sainte-Justine
Montreal, QC, Canada

Cedric Manlhiot, Ph.D.
Blalock-Taussig-Thomas Congenital Heart Center at Johns Hopkins University
Baltimore, MD
cmanlhi1@jhmi.edu

for the International Kawasaki Disease Registry

A list of the International Kawasaki Disease Registry investigators is provided in the Supplementary Appendix, available at NEJM.org.

The contents of this letter 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 and Human Development or the Office of the Director, National Institutes of Health.

Supported by a grant (R61HD105591) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Office of the Director, National Institutes of Health.

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on March 22, 2023, at NEJM.org.

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DOI: 10.1056/NEJMc2215074