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BRIEF REPORT

Impact of Severe Acute Respiratory Syndrome Coronavirus 2 Variants on Short- and Mid-term Cardiac Outcomes in Multisystem Inflammatory Syndrome in Children

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Cardiac outcomes of 131 children with multisystem inflammatory syndrome (MIS-C) were examined. The majority of the cohort was male (66.4%) and half were Black (49.6%). Cardiac involvement was evident in 25% of the cohort at diagnosis. Favorable short- and mid-term outcomes were documented on follow-up, irrespective of the severe acute respiratory syndrome coronavirus 2 variants causing the infection.

Keywords. cardiac; MIS-C; SARS-CoV-2.

Multisystem inflammatory syndrome in children (MIS-C) is a hyper-inflammatory condition temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with a significant clinical overlap with entities like Kawasaki disease (KD) and toxic shock syndrome [1–3]. As of 3 October 2022, more than 14.8 million children have been infected with SARS-CoV-2 and 9000 children have been diagnosed with MIS-C in the United States [4]. While MIS-C is still considered a rare sequela of SARS-CoV-2 infection, concern remains for long-term cardiac outcomes due to overlap in clinical presentation of and treatment approaches used for KD [5–7]. Acutely, KD has been known to cause arrhythmias, myocardial inflammation (50%–70%), valvular lesions (23%–27%), and coronary artery (CA) abnormalities (~4%–8% after treatment with intravenous immunoglobulin), ranging from dilatation only to aneurysms of variable sizes and characteristics. On long-term follow-up, CA events (thrombosis, stenosis, myocardial infarction, and death) occur in a subset of children with KD, predominantly in those with giant aneurysms [8]. Although the pathogenesis of MIS-C is not known, it is hypothesized to be a result of dysregulated immune response to SARS-CoV-2 [9–16] leading to myocardial dysfunction and CA involvement [16, 17].

While a majority of pediatric coronavirus disease 2019 (COVID-19) cases are mild compared to those in adults, infection rates and the frequency of MIS-C have varied based on the circulating SARS-CoV-2 variants [18–20]. The objective of this study is to describe acute cardiac involvement and short- and mid-term cardiac outcomes in children with MIS-C that followed 3 different waves of the SARS-CoV-2 infection during the first 2 years of the pandemic.

METHODS

Early during the SARS-CoV-2 pandemic, a multidisciplinary clinic was established to monitor children with MIS-C hospitalized at Children's of Alabama/University of Alabama at Birmingham (UAB) and approved by the UAB institutional review board. Children diagnosed with MIS-C, based on the Centers for Disease Control and Prevention (CDC) criteria, were followed in clinic at 4–6 weeks and 6 months after diagnosis with serial laboratory tests, electrocardiography (ECG), and echocardiography (ECHO) [1]. Demographic, clinical, and laboratory data and findings from studies to assess cardiac involvement were collected and analyzed.

Troponin I >0.04 ng/mL and B-type natriuretic peptide (BNP) >100 pg/mL were considered to be outside of normal range. ECG data were coded as normal or abnormal. Data on the following ECHO parameters were collected: (1) qualitative left ventricular (LV) systolic function (normal or decreased); (2) quantitative LV systolic function (ejection fraction): normal (>54%), mild decrease (45%–54%), moderate decrease (35%–44%), or severe (<35%); (3) pericardial effusion (present vs absent); and (4) CA aneurysm (z score <2.5 vs ≥2.5).

The study cohort is divided into 3 groups based on the timing of hospitalization for MIS-C: (1) group 1, children diagnosed between April and October 2020 (predominant SARS-CoV-2 variant was Wuhan); (2) group 2, November 2020 through July 2021 (predominant variant, Alpha/B.1.1.7); and (3) group 3, August–December 2021 (predominant variant, Delta/B.1.617.2).

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Statistical Analysis

The frequency and extent of laboratory, ECG, and ECHO abnormalities for the entire cohort were compiled and compared between the 3 groups. Continuous variables were compared by Kruskal-Wallis test, and χ^2 or Fisher exact test was used to compare categorical variables. *P* value <.05 was considered statistically significant. GraphPad Prism 8 software was used for statistical analysis.

RESULTS

Between April 2020 and December 2021, 131 children evaluated at Children's of Alabama met the CDC criteria for MIS-C. Groups 1, 2, and 3 included 32, 61, and 38 children, following infections caused by the Wuhan, Alpha, and Delta variants, respectively. Of these, 103 (78.6%) were followed at a median of 6 weeks (95% confidence interval [CI], 5–6 weeks) from diagnosis for short-term follow-up, and 47 of 131 (35.9%) at 7 months (95% CI, 6–7 months) for mid-term follow-up.

Demographic, laboratory, ECG, and ECHO findings at MIS-C diagnosis for the entire cohort and the 3 groups are summarized in Table 1. In brief, the median age for the entire cohort was 10 years (range, 0.75–17 years) and the majority affected were male (66.4%) and Black (49.6%) in the entire cohort and in each individual group. Troponin I levels were elevated in more than half (68/129 [52.7%]), and BNP was elevated in 82% of children at diagnosis. At hospital admission, 48 of 131 (36.6%) children required vasopressors to maintain blood pressure for a median of 24 hours. There were no deaths. BNP and troponin I levels for all children obtained at short- and mid-term follow-up were within the normal range, irrespective of assignment to group 1, 2, or 3.

A quarter of the cohort in whom ECGs were obtained during hospitalization had an abnormal finding (28/112 [25%]), with no significant differences between the 3 groups for frequency of ECG abnormalities ($P = .14$). A majority of those in whom ECG was obtained during short-term (92/93 [98%]) and mid-term (41/41 [100%]) follow-up had normal ECG findings.

ECHO was obtained within 2 days of hospital admission at diagnosis with abnormal findings observed in less than half the cohort (54/131 [41.2%]). Decreased LV function was reported in a quarter of this cohort (33/131 [25%]), with no significant differences between the 3 groups (25% in group 1, 23% in group 2, and 29% in group 3; $P = .79$). Trivial to small pericardial effusions were detected in 29 of 131 (22%) children. CA aneurysms (*z* score ≥2.5) were detected in 3 of 131 (2.35%) children. All children followed at short-term and mid-term had normal ECHO findings. The 3 children with CA aneurysms at diagnosis had normal laboratory, ECG, and ECHO findings on follow-up. The laboratory, ECG, and ECHO data at short- and mid-term follow-up are summarized in Table 2.

DISCUSSION

To date, short- and mid-term cardiac outcomes are only available from small cohorts of MIS-C [21–25]. In this study, we document good cardiac outcome with normalization of laboratory, ECG, and ECHO abnormalities in most of the 131 children followed, within 5–6 weeks following MIS-C.

Consistent with published data, we document Black predominance in the entire cohort and within each individual group [26]. We also observed shorter hospitalization durations for children with MIS-C following infection with the Delta variant (group 3) compared to the other 2 groups (3.5 days vs 5 days; $P = .0004$). Contrary to previous reports [27], we did not observe an increased frequency or severity of MIS-C–related hospitalizations over time (32, 61, and 38 in groups 1, 2, and 3, respectively), likely due to differences among SARS-CoV-2 variants or yet-undetermined protective factors like vaccination and/or natural infection.

Evidence of myocarditis in our cohort was based on elevated BNP and troponin I levels, considered surrogate biomarkers of myocardial injury [3, 17, 25, 28]. The majority had elevated troponin I and BNP levels at diagnosis (52.7% and 82%, respectively), without significant differences between the 3 groups. Similarly, no differences in qualitative or quantitative parameters of LV function were observed. Only 3 children in this cohort (3/131 [2.3%]) developed CA aneurysms (*z* score ≥2.5) with involvement of multiple coronaries, but recovered completely in 6 weeks, unlike studies that reported persistent abnormalities in 3%–50% [17, 22–24, 29]. These differences could be due to inclusion of children with only CA aneurysms (*z* score ≥2.5), rather than dilatation. We chose to use this *z* score cutoff since most long-term morbidity and mortality in KD is associated with aneurysms rather than dilatation alone. This allows us to focus on findings with a stronger correlation to adverse cardiac outcomes and prevents overestimation of CA involvement in MIS-C.

We did not compare clinical/cardiac outcomes in this cohort according to differences in therapeutic interventions since cardiac involvement (laboratory, vasopressor use, ECG, and ECHO) was assessed at presentation, prior to administration of any therapeutics. Additionally, recent studies have reported no significant differences in cardiac outcomes irrespective of treatment modality utilized [24, 30, 31].

Two small studies that focused on ECG abnormalities in MIS-C found that 19%–56% of children at presentation developed transient ECG abnormalities [32, 33]. Since the most common ECG abnormality in this cohort was nonspecific ST-T wave changes (26/112 [23.2%]) but resolved on follow-up, the clinical significance remains unclear.

The major limitation of this study is the lack of mid-term follow-up in 64% of the cohort. Of the 131 children in the cohort, 28 (21.4%) children did not have follow-up information

Table 1. Demographic, Laboratory, Electrocardiogram, and Echocardiogram Findings at Diagnosis of Multisystem Inflammatory Syndrome in Children

Characteristic	Entire Cohort	Timing of Hospitalization			*P* Value
		Group 1: Wuhan (Apr–Oct 2020)	Group 2: Alpha (B.1.1.7) (Nov 2020–Jul 2021)	Group 3: Delta (B.1.617.2) (Aug–Dec 2021)	
Cohort size, No.	131	32	61	38	
Age, y, median (95% CI)	10 (8.8–12)	12 (10–13)	10 (6.9–12)	8.4 (7–11)	.3
Sex					
Male	87 (66.4%)	18 (56%)	43 (70.5%)	26 (68.4%)	.7
Female	44 (33.6%)	14 (43.8%)	18 (29.5%)	12 (31.6%)	
Race/ethnicity					
Black	65 (49.6%)	16	34	15	.5
White, Hispanic	16 (12%)	5	3	8	
White, non-Hispanic	48 (36.6%)	11	23	14	
Other	2 (1.5%)	0	1	1	
Hospitalization, d, median (IQR)	4 (3–6)	5 (4–8.8)	5 (4–6)	3.5 (3–5)	1 vs 3 = .0004 1 vs 2 = ns 2 vs 3 = .0035
Laboratory analysis					
SARS-CoV-2 PCR positive	33/131 (25.2%)	9/32 (28.1%)	23/61 (37.7%)	1/38 (2.6%)	.7
SARS-CoV-2 IgG positive	123 (93.9%)	25/32 (78%)	59/61 (96.7%)	38/38 (100%)	.9
Elevated Troponin (>0.04 ng/mL)	68/129 (52.7%)	20/32 (62.5%)	30/59 (50.84%)	18/38 (47.4%)	.4
Median troponin peak, ng/mL	0.05 (0.01–216)	0.095 (0.01–9)	0.05 (0.01–2.7)	0.04 (0.01–216)	.14
Elevated BNP (>100 pg/mL)	108 (82.4%)	27/32 (84.4%)	50/61 (81.9%)	31/38 (81.6%)	.94
Median BNP, pg/mL	568 (10–6376)	804 (10–4373)	513 (10–6376)	676 (10–3640)	.65
Vasopressor use	48/131 (36.6%)	14/32 (43.7%)	17/61 (27.9%)	17/38 (44.7%)	.15
ECG					
Abnormal	28/112 (25%)	7/29 (24%)	16/48 (33.3%)	5/35 (14.3%)	.14
NS ST-T wave	26	6	15	5	
1° AV block	1	1	0	0	
RBBB	1	0	1	0	
ECHO					
Abnormal	54/131 (41.2%)	16/32 (50%)	24/61 (39.3%)	14/38 (36.8%)	.5
LV systolic dysfunction	33/131 (25.2%)	8/32 (25%)	14/61 (22.9%)	11/38 (28.9%)	.79
Mild	21	5	9	7	
Moderate	9	2	4	3	
Severe	3	1	1	1	
Median EF	60%	61%	60%	59%	.52
Pericardial effusion	29/131 (22.1%)	10/32 (31.2%)	13/61 (21.3%)	6/38 (15.8%)	.29
Dilated CA (*z* score >2.5)	3/131 (2.3%)	2/32 (6.2%)	0/61 (0%)	1/38 (2.6%)	

Abbreviations: AV, atrioventricular; BNP, B-type natriuretic peptide; CA, coronary artery; CI, confidence interval; ECG, electrocardiogram; ECHO, echocardiogram; EF; ejection fraction; IgG, immunoglobulin G; IQR, interquartile range; LV, left ventricle; ns, not significant; NS ST-T, nonspecific ST and T wave; PCR, polymerase chain reaction; RBBB, right bundle branch block; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

after discharge. Of children with short-term follow-up, 56 of 103 (54%) were documented to have normal ECHO and did not follow-up at mid-term. We believe the attrition in this study is due to the remarkable improvement in cardiac findings in most children in this cohort and likely the belief by families of the overall well-being of their children. Lack of a control group and cardiac magnetic resonance imaging (MRI) data are few other limitations of our study. The cardiac findings described in our cohort are consistent with findings described in smaller studies of MIS-C that included children with KD as controls, suggesting no significant differences in children presenting with MIS-C across institutions/regions [16, 17, 22]. Given the overall good cardiac prognosis based on ECHO, it is unlikely that cardiac MRI would have provided significant additional information. Also, obtaining cardiac MRI in all children with cardiac involvement is cost-prohibitive.

Unfortunately, SARS-CoV-2 variant sequencing to identify the infecting variant to ensure children are assigned to the correct group was not performed as part of this study. Since most cases of MIS-C follow mild/asymptomatic infections, respiratory samples to perform viral sequencing were not available. Instead, we divided the cohort into 3 groups based on CDC reported timelines for when the given SARS-CoV-2 variant was responsible for >50% of infections across the United States, and chose time points >4 weeks after the peak to account for the temporal association between COVID-19 and MIS-C. While this arbitrary

Table 2. Short- and Mid-term Cardiac Follow-up

Cardiac Study	Entire Cohort	Group 1: Wuhan	Group 2: Alpha (B.1.1.7)	Group 3: Delta (B.1.617.2)
No. at MIS-C diagnosis	131	32	61	38
Short-term follow-up				
No. at follow-up	103/131 (78.6%)	28/32 (87.5%)	46/61 (75.4%)	29/38 (76.3%)
BNP				
Obtained	93/103 (90.2%)	22/28 (78.6%)	44/46 (95.7%)	27/29 (93.1%)
Normal	100%	100%	100%	100%
Troponin				
Obtained	90/103 (87.3%)	19/28 (67.9%)	44/46 (95.7%)	27/29 (93.1%)
Normal	100%	100%	100%	100%
ECG				
Obtained	93/103 (90.3%)	24/28 (85.7%)	44/46 (95.6%)	25/29 (86.2%)
Normal	92/93 (98.9%)	(23/24) 95.8%	100%	100%
Abnormal (NS ST-T abnormality)	1/93 (1%)	(1/24) 4.2%	0%	0%
ECHO				
Obtained	103/103 (100%)	28/28 (100%)	46/46 (100%)	29/29 (100%)
Normal	100%	100%	100%	100%
Mid-term follow-up				
No. at follow-up	47/131 (35.87%)	13/32 (40.6%)	26/61 (42.6%)	8/38 (21%)
BNP				
Obtained	45/47 (95.7%)	12/13 (92.3%)	26/26 (100%)	7/8 (87.5%)
Normal	100%	100%	100%	100%
Troponin				
Obtained	45/47 (95.7%)	12/13 (92.3%)	26/26 (100%)	7/8 (87.5%)
Normal	100%	100%	100%	100%
ECG				
Obtained	41/47 (87.2%)	13/13 (100%)	21/26 (80.8%)	7/8 (87.5%)
Normal	100%	100%	100%	100%
ECHO				
Obtained	47/47 (97.6%)	13/13 (100%)	26/26 (100%)	8/8 (100%)
Normal	100%	100%	100%	100%

Abbreviations: BNP, B-type natriuretic peptide; ECG, electrocardiogram; ECHO, echocardiogram; MIS-C, multisystem inflammatory syndrome in children; NS ST-T, nonspecific ST and T wave.

classification may have led to misclassification of some children, we think this approach was appropriate for most children included in this cohort.

In conclusion, in this single-center prospective cohort study of children with MIS-C, we demonstrate favorable cardiac outcomes without any differences in the frequency and severity of cardiac involvement during the acute, short-term, and mid-term follow-up, irrespective of infection following different SARS-CoV-2 variants (Wuhan vs Alpha vs Delta).

Notes

Author contributions. S. P. conceptualized and designed the study, was responsible for clinical follow-up, coordinated and supervised data collection, carried out the initial analysis, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Suresh Boppana conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript for important intellectual content, and revised the manuscript. Ca. H. and J. C. independently reviewed electrocardiograms and echocardiograms for the study and reviewed and revised the manuscript. C. T., Sus. B., and M. B. designed data collection instruments, collected data, and reviewed and revised the manuscript. C. S. and A. Y. supervised clinic follow-up and data management, and reviewed and revised the manuscript. C. P., S. J., S. R., and Ce. H. clinically managed patients in the clinic, supervised data collection, and reviewed and revised the manuscript.

Patient consent. The design of the work was approved by local ethical committees and conforms to standards currently applied in the country of origin, and includes the name of the authorizing body stated in the manuscript. This study does not include factors necessitating patient consent.

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