RESEARCH

MIS-C across three SARS-CoV-2 variants: Changes in COVID-19 testing and clinical characteristics in a cohort of U.S. children

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Abstract

As new variants of SARS-Co-V 2 have emerged over time and Omicron sub-variants have become dominant, the severity of illness from COVID-19 has declined despite greater transmissibility. There are fewer data on how the history, diagnosis, and clinical characteristics of multisystem inflammatory syndrome in children (MIS-C) have changed with evolution in SARS-CoV-2 variants. We conducted a retrospective cohort study of patients hospitalized with MIS-C between April 2020 and July 2022 in a tertiary referral center. Patients were sorted into Alpha, Delta, and Omicron variant cohorts by date of admission and using national and regional data on variant prevalence. Among 108 patients with MIS-C, significantly more patients had a documented history of COVID-19 in the two months before MIS-C during Omicron (74%) than during Alpha (42%) (p = 0.03). Platelet count and absolute lymphocyte count were lowest during Omicron, without significant differences in other laboratory tests. However, markers of clinical severity, including percentage with ICU admission, length of ICU stay, use of inotropes, or left ventricular dysfunction, did not differ across variants. This study is limited by its small, single-center case series design and by classification of patients into era of variant by admission date rather than genomic testing of SARS- CoV-2 samples.

Conclusion: Antecedent COVID-19 was more often documented in the Omicron than Alpha or Delta eras, but clinical severity of MIS-C was similar across variant eras.

What is Known:
• *There has been a decrease in incidence of MIS-C in children despite widespread infection with new variants of COVID-19.*
• *Data has varied on if the severity of MIS-C has changed over time across different variant infections.*

What is New:
• *MIS-C patients were significantly more likely to report a known prior infection with SARS-CoV-2 during Omicron than during Alpha.*
• *There was no difference in severity of MIS-C between the Alpha, Delta, and Omicron cohorts in our patient population.*

Keywords COVID-19 · MIS-C · SARS-CoV-2 · Children

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Introduction

Recent data suggest that the characteristics of multisystem inflammatory syndrome in children (MIS-C) may have changed as new variants of SARS-CoV-2 have emerged and become the predominant strains [1]. Data from the Centers for Disease Control and Prevention (CDC) show surges in the number of cases of MIS-C during January 2021, October 2021, and January 2022, with highest incidence in January 2021 despite lower incidence of COVID-19 during this time than during January 2022 [2]. A study in Israel found that MIS-C during the Omicron wave has been less severe than

during the Alpha or Delta waves [3], while data from South Africa and Europe suggested no difference in severity across the variant waves [4, 5]. Reports have also shown a lower incidence of MIS-C after Omicron [5–8]. The diagnosis of MIS-C, however, remains a challenge. Indeed, signs and symptoms of fever, hypotension, rash, and gastrointestinal symptoms are nonspecific and may be seen at presentation in not only MIS-C, but also Kawasaki disease, toxic shock syndrome, viral illness, sepsis, and other entities. A key feature that distinguishes MIS-C from other illnesses is its link to COVID-19. Diagnosis of MIS-C requires at least 1 of 4 criteria to establish a temporal link to COVID-19: positive SARS-CoV-2 polymerase chain reaction (PCR), positive antigen test, positive serology, or a recent COVID-19 exposure [9]. Since the CDC published criteria for MIS-C in April 2020 [9], the predominant SARS-CoV-2 variant, frequency of exposure and infection, and testing availability each have changed. There is little data on how MIS-C patients meet the COVID-19 criteria and if that has changed over time. There is also limited data on if and how the clinical characteristics of MIS-C have changed over time in patients in the United States with the emergence of new variants. We sought to explore how the diagnosis of prior COVID-19 in children with MIS-C and the clinical characteristics of MIS-C have changed across the eras of three SARS-CoV-2 variant waves.

Methods

We conducted a single-center retrospective cohort study of patients hospitalized with MIS-C between April 2020 and July 2022. All patients admitted to our center between April 2020 and July 2022 with suspicion for MIS-C were screened for inclusion. Cases with a clinical diagnosis of MIS-C were then adjudicated by both an expert panel at our center and the Massachusetts Department of Public Health based on the 2020 CDC case definition of MIS-C [9]. Patients who were adjudicated as having MIS-C by both our center's expert panel and the Department of Public Health were included in this series, with no additional exclusion criteria.

Clinical data were manually extracted and laboratory data were automatically downloaded from the electronic medical records of each patient. Variables were selected based on the standard initial laboratory evaluation for patients with MIS-C in our hospital, focusing on tests that are frequently abnormal, and clinical features that would indicate the variation in severity, complications, and treatment course [10]. The variables abstracted from the patients' charts include the basis for a diagnosis of previous COVID-19 (i.e., positive PCR or antigen test for SARS-CoV-2 within the preceding two months and the date of positive test, household exposure to COVID-19 within the preceding two months, and positive PCR and/or nucleocapsid antibody testing results on admission); sociodemographic data (i.e., age, sex, race, body mass index, and zip code); clinical features (i.e., days of fevers prior to presentation, symptoms at presentation, lowest left ventricular ejection fraction during hospitalization, highest coronary artery z-score during hospitalization, intensive care unit admission, hospital length of stay, and treatments received); and laboratory tests on admission (i.e., blood counts, inflammatory markers, and markers of kidney and liver function). The use of inotropes, left ventricular dysfunction, coronary involvement, and intensive care unit admission and length of stay were used as markers of severity of illness. Acute kidney injury was defined by creatinine level for age: < 4 weeks: > 1.59 mg/dL, 4 weeks–< 1 year: > 0.55 mg/dL, 1–10 years: > 1.13 mg/dL, and ≥ 11 years: > 1.59 mg/dL [11]. Lymphocytopenia was defined as absolute lymphocyte count less than 1500×10^3 cells/µL. Childhood opportunity index (COI, scale 1–100) was computed from zip codes [12].

The SARS-CoV-2 variant was assigned according to patient admission dates based upon CDC data on variant prevalence: Alpha (April 1, 2020 to June 30, 2021), Delta (July 1, 2021 to December 31, 2021), and Omicron (January 1, 2022 to July 31, 2022) [13]. We compared national data to regional genomic testing of respiratory swabs and wastewater, which estimated the date that each SARS-CoV-2 variant became dominant in our region as March 1, 2020 for Alpha, June 28, 2021 for Delta, and December 17, 2021 for Omicron [14–16]. These data suggest that Alpha became predominant one month earlier, Delta at about the same time, and Omicron about two weeks earlier in local circulation than national circulation. Sensitivity analysis was then performed using start dates of four weeks after the variant became locally dominant to account for an approximate one month delay between COVID-19 and MIS-C: Alpha (April 1, 2020 to July 27, 2021), Delta (July 28, 2021 to January 16, 2022), and Omicron (January 17, 2022 to July 8, 2022). Variant testing of individual patient samples was not performed. Categorical variables were summarized as frequencies and percentages and compared across variant eras using Fisher's exact test. Continuous variables were summarized with medians and interquartile ranges and compared using the Kruskal–Wallis test. Statistical significance was defined as a p-value ≤ 0.05. When significant differences across eras were identified, post hoc comparisons were performed using a Bonferroni correction. Missing data were excluded from relevant comparison. Our Institutional Review Board reviewed the study and waived the need for individual informed consent.

Results

Among 108 patients who met the case definition for MIS-C, 69 (64%) were admitted during the Alpha wave, 16 (15%) during the Delta wave, and 23 (21%) during the Omicron wave. Among 23 patients admitted during the Omicron wave, 21 (91%) were admitted when BA.1 was the predominant variant (January 1, 2022 to March 5, 2022) [17]. Median age at diagnosis was 8 [interquartile range (IQR), 5 to 12] years, 46% were female, and 47% were underrepresented minorities (self-identified Black and/or Hispanic), with no significant differences among the cohorts in age, race, ethnicity, or sex (Table 1). The median COI was 68 [IQR 28–86], and 52% of patients were overweight or obese (body mass index (BMI) $\geq 85^{th}$ percentile). Overall, 49% of patients had a chronic medical problem, with the most prevalent conditions being obesity (30%), asthma (15%), and mental health conditions (6%). The MIS-C cases during each variant predominant period did not differ significantly in COI, BMI percentile, or chronic medical problems.

All 108 MIS-C patients (100%) had positive nucleocapsid SARS-CoV-2 serology upon admission. A documented history of COVID-19 (by patient self-report of a positive PCR or antigen test or records of a positive test in our medical record) in the preceding two-month period differed significantly across the eras (p = 0.03) (Table 2); the proportion was significantly higher during Omicron (74%) than during Alpha (42%). Patients without a recent positive test for COVID-19 were tested with SARS-CoV-2 PCR at the time of admission (n = 94 total, 62 during Alpha, 15 during Delta, 17 during Omicron). MIS-C cases in the three variant eras differed significantly (p = 0.01) with respect to PCR positivity during the MIS-C episode, with significantly more testing positive during Alpha (31%) than during Omicron (0%). Among those without a laboratory-documented history of COVID-19, the cohorts did not differ significantly with respect to reported household COVID-19 exposure in the preceding two months (53% during Alpha, 38% during Delta, 67% during Omicron). Among 23 patients with MIS-C in the Omicron wave, 21 (91%) had either laboratory-documented COVID-19 (n = 17) or a household COVID-19 exposure (n = 4). Because patients with a recent documented episode of COVID-19 were not tested with repeat PCR, we performed a second analysis in which patients who were PCR positive at admission were combined with those who had a documented history of COVID-19 in the previous two months. When patients who were PCR positive at admission were combined with the patients who had a positive test in the two months prior to admission, there was no significant difference between cohorts (62% during Alpha, 50% during

Table 1 Socio-Demographics of MIS-C Patients

	Total (n = 108)	Alpha (n = 69)	Delta (n = 16)	Omicron (n = 23)	P Value
Age at MIS-C diagnosis (years)	8 [5, 12]	9 [5, 13]	8 [6, 9]	6 [5, 9]	0.11
Sex female	50 (46%)	29 (42%)	6 (38%)	15 (65%)	0.11
Race					
White	35 (32%)	25 (36%)	5 (31%)	5 (22%)	0.29
Black or African American	24 (22%)	12 (17%)	5 (31%)	7 (30%)	
Asian	2 (2%)	1 (1%)	0 (0%)	1 (4%)	
American Indian or Alaska native	1 (1%)	1 (1%)	0 (0%)	0 (0%)	
Other	25 (23%)	18 (26%)	5 (31%)	2 (9%)	
Unknown / declined to answer	21 (19%)	12 (17%)	1 (6%)	8 (35%)	
Hispanic or Latino ethnicity					
Yes	30 (28%)	21 (30%)	6 (38%)	3 (13%)	0.30
No	57 (53%)	37 (54%)	7 (44%)	13 (57%)	
Unknown / declined to answer	21 (19%)	11 (16%)	3 (19%)	7 (30%)	
Black and/or Hispanic	51 (47%)	31 (45%)	10 (63%)	10 (43%)	0.48
Body mass index (BMI) percentile (n = 104, 65, 16, 23)	86 [54, 97]	87 [54, 97]	91 [66, 98]	66 [29, 93]	0.13
BMI >85th percentile (n = 104, 65, 16, 23)	54/104 (52%)	38/65 (58%)	9/16 (56%)	7/23 (30%)	0.071
Child opportunity index	68 [28, 86]	66 [31, 82]	36 [15, 87]	82 [46, 95]	0.11
Any chronic medical problem	53 (49%)	34 (49%)	8 (50%)	11 (48%)	1.0
Obesity	32 (30%)	22 (32%)	6 (38%)	4 (17%)	0.33
Asthma	16 (15%)	9 (13%)	1 (6%)	6 (26%)	0.23
Mental health	6 (6%)	3 (4%)	1 (6%)	2 (9%)	0.58

Data are summarized as number (percent) for categorical variables, and as median [interquartile range] for continuous variables. Comparisons are made across the three variant groups using either Fisher's exact test or the Kruskal-Wallis test

Table 2 COVID-19 Assessment by Era of Variant

COVID-19 Assessment	Total (n = 108)	Alpha (n = 69)	Delta (n = 16)	Omicron (n = 23)	P Value
Documented[a] COVID-19 in the 2 months prior to admission	54 (50%)	29 (42%)	8 (50%)	17 (74%)	0.030[c]
Household COVID-19 exposure in patients without documented COVID-19 in the 2 months prior to admission (n = 54, 40, 8, 6)	28 (52%)	21 (53%)	3 (38%)	4 (67%)	0.61
PCR positive results on the day of admission (n = 94, 62, 15, 17)	21/94 (22%)	19/62 (31%)	2/15 (13%)	0/17 (0%)	0.010[d]
Documented COVID-19 in 2 months prior and/or PCR positive results on day of admission	67 (62%)	42 (61%)	8 (50%)	17 (74%)	0.34
Days from COVID-19 illness to admission (n = 54, 29, 8, 17)	34 [30, 43][b]	32 [27, 43]	36 [31, 40]	39 [33, 49]	0.34
Days from COVID-19 exposure to admission (n = 24, 18, 3, 3)	31 [30, 60]	41 [30, 60]	30 [29, 60]	30 [30, 31]	0.46

Data are summarized as number (percent) for categorical variables, and as median [interquartile range] for continuous variables. Comparisons are made across the three variant groups using either Fisher's exact test or the Kruskal-Wallis test

[a]Documented by patient self-report of a recent positive antigen or PCR test or records of a positive PCR test in our medical record

[b]Numbers in brackets represent interquartile ranges

[c]Applying a Bonferroni correction, rates of documented prior COVID-19 was lower during Alpha than Omicron

[d]Applying a Bonferroni correction, PCR positivity was higher during Alpha than Omicron

Delta, and 74% during Omicron, $p = 0.34$). There was no significant difference among variant eras in median days between MIS-C onset and either documented COVID-19 or household exposure to an individual with COVID-19; these intervals in the combined variant groups were 34 [IQR 30–43] days and 31 [IQR 30–60] days, respectively.

Characteristics of MIS-C cases in each variant wave are summarized in Table 3. Median days of fever prior to presentation varied between groups ($p = 0.03$), with significantly fewer days of fever during Alpha (4 days [IQR 3–5]) than during Omicron (5 days [IQR 4–6]). Significantly fewer patients had hypotension on admission during Alpha than during Delta (39% and 81% respectively, $p = 0.003$); this significant difference persisted after adjusting for days of fever at time of presentation. The waves did not differ significantly in the percentages who were admitted to an intensive care unit (ICU) (41%, 31%, and 52%, respectively), length of ICU stay (5, 4, and 4 days, respectively), or use of inotropes (32%, 31%, and 35%, respectively). The percentage with left ventricular dysfunction on echocardiogram (ejection fraction ≤ 55%) (52%, 38%, 43%, respectively, $p = 0.52$) or coronary dilation (maximum coronary Z-score ≥ 2.5) (17%, 6%, 22%, respectively, $p = 0.48$) were also similar across the waves. Among laboratory values at presentation, absolute lymphocyte count was higher during Alpha (1266×10^3 cells/μL [IQR 761- 2067) than during Omicron (610×10^3 cells/μL [IQR 490–980]) ($p = 0.004$), and platelet counts were higher during Delta (217×10^3 cells/μL [IQR 177–264]) than during Omicron (145×10^3 cells/μL [IQR 95–221]) ($p = 0.026$) (Table 4). There were no significant differences in total white blood cell count, hemoglobin, absolute neutrophil count, C-reactive protein, blood

urea nitrogen, creatinine, albumin, or alanine transaminase. The percentage of patients with acute kidney injury did not differ significantly between cohorts (Alpha 6%, Delta 6%, Omicron 9%, $p = 0.85$). A significantly higher proportion of patients had lymphocytopenia on admission during Omicron (77%) than during Alpha (35%) ($p = 0.002$). Median hospital length of stay was significantly shorter during Delta (3 days, [IQR 2–4]) than during Alpha (5 days [IQR 4–8]) or during Omicron (4 days [IQR 3–7]) ($p = 0.002$). There was no significant difference between Alpha, Delta, and Omicron waves in the percentage of patients who received treatment with intravenous immunoglobulin (IVIG) (94%, 81%, and 100%, respectively, $p = 0.077$), steroids (86%, 75%, and 96%, respectively, $p = 0.20$), or anakinra (17%, 19%, and 9%, respectively, $p = 0.57$) while hospitalized or who were discharged on steroid therapy (84%, 75%, and 96%, respectively, $p = 0.20$). Significantly fewer patients were discharged on aspirin during Delta than during Omicron (63%, and 100%, respectively, $p = 0.005$) [18].

In our sensitivity analysis, when patients were sorted into Alpha, Delta, and Omicron cohorts based upon a four-week delay from when the variant became regionally dominant to admission date, markers of severity and testing data did not change in significance compared to the original analysis (Online Resource 1). In contrast to the original analysis, the variant cohorts differed significantly in the percent of patients with BMI > 85 percentile ($p = 0.026$), treated with steroids ($p = 0.028$), and discharged on steroids ($p = 0.040$), as well as in levels of alanine transaminase ($p = 0.040$). The cohorts no longer differed significantly in platelet counts ($p = 0.17$).

Table 3 Clinical Characteristics and Treatments of MIS-C Patients

	Total (n = 108)	Alpha (n = 69)	Delta (n = 16)	Omicron (n = 23)	P Value
Symptoms or Clinical Features at Presentation					
Total days of fever	5 [3, 6][a]	4 [3, 5]	5 [4, 7]	5 [4, 6]	0.031[c]
Rash / mucocutaneous, including conjunctivitis	65 (60%)	38 (55%)	10 (63%)	17 (74%)	0.28
Gastrointestinal (nausea, vomiting, diarrhea, abdominal pain)	87 (81%)	52 (75%)	16 (100%)	19 (83%)	0.060
Hypotension[b]	55 (51%)	27 (39%)	13 (81%)	15 (65%)	0.003[d]
Neck pain	25 (23%)	12 (17%)	6 (38%)	7 (30%)	0.14
Upper respiratory infection (congestion, rhinorrhea, sore throat, cough)	37 (34%)	25 (36%)	3 (19%)	9 (39%)	0.41
Shortness of Breath	3 (3%)	3 (4%)	0 (0%)	0 (0%)	0.74
Neurologic (headache, weakness, confusion, seizures)	30 (28%)	20 (29%)	5 (31%)	5 (22%)	0.82
Acute kidney injury	7 (6%)	4 (6%)	1 (6%)	2 (9%)	0.85
Markers of Severity					
Inotropes	35 (32%)	22 (32%)	5 (31%)	8 (35%)	0.96
Left ventricular dysfunction (ejection fraction < 55%) (n = 107, 68, 16, 23)	52/107 (48%)	36/68 (52%)	6/16 (38%)	10/23 (43%)	0.52
Coronary involvement (z-score ≥ 2.5)	18 (17%)	12 (17%)	1 (6%)	5 (22%)	0.49
Any intensive care unit (ICU) admission	45 (42%)	28 (41%)	5 (31%)	12 (52%)	0.42
ICU length of stay (days), if admitted to ICU (n = 45, 28, 5, 12)	4 [3, 7]	5 [3, 7]	4 [3, 7]	4 [3, 5]	0.55
Hospital length of stay (days)	5 [3, 8]	5 [4, 8]	3 [2, 4]	4 [3, 7]	0.002[e]
Treatments					
Intravenous immunoglobulin (IVIG)	101 (94%)	65 (94%)	13 (81%)	23 (100%)	0.077
Steroids	93 (86%)	59 (86%)	12 (75%)	22 (96%)	0.20
Anakinra	18 (17%)	13 (19%)	3 (19%)	2 (9%)	0.57
Discharge on aspirin	91 (84%)	58 (84%)	10 (63%)	23 (100%)	0.005[f]
Discharge on steroids	92 (85%)	58 (84%)	12 (75%)	22 (96%)	0.20

Data are summarized as number (percent) for categorical variables, and as median [interquartile range] for continuous variables. Comparisons are made across the three variant groups using either Fisher's exact test or the Kruskal-Wallis test

[a]Numbers in brackets represent interquartile ranges

[b]Hypotension defined by clinician documentation of hypotension in the medical record

[c]Applying a Bonferroni correction, there were fewer days of fever during Alpha than during Omicron

[d]Applying a Bonferroni correction, hypotension was less frequent during Alpha than during Delta

[e]Applying a Bonferroni correction, hospital length of stay was shorter in Delta than both Alpha and Omicron

[f]Applying a Bonferroni correction, discharge on aspirin was less frequent during Delta than Omicron

Discussion

In this single-center retrospective series of children with MIS-C across three variant eras, we demonstrated evolution in how children met the MIS-C diagnostic criterion of past COVID-19 infection. Specifically, a greater percentage of children in the Omicron era had laboratory documentation of antecedent COVID-19 by PCR or antigen testing in the expected window prior to MIS-C. The higher percentage of patients with a documented history of recent COVID-19 in the Omicron era, compared with Alpha or Delta eras, likely reflects the improved availability of PCR and home antigen testing, trends that are expected to continue. In contrast, fewer patients had positive PCR testing at the time of MIS-C admission in the Omicron era. This could suggest a refined ability to discriminate acute COVID-19 from MIS-C or shorter persistence of viral genome after infection with the Omicron variant, though not all patients had PCR testing at the time of admission [19]. Because patients who had recent documented COVID-19 were not tested at the time of admission, there could be bias towards lower PCR positivity during Omicron, and indeed there was no significant difference in the combined group of patients who were either PCR positive at admission or had a positive test in the two months prior to admission. All cases in our series had positive nucleocapsid serology, but serology alone in the current era may be inadequate to determine timing of COVID-19 relative to MIS-C onset. Indeed, as of August 2022, ~ 86% of US children had had COVID-19 based upon antibodies, a percentage that is likely to continue to grow [20]. Taken

Table 4 Laboratory Values at Admission of MIS-C Patients

Laboratory Values at Admission	Total (n = 108)	Alpha (n = 69)	Delta (n = 16)	Omicron (n = 23)	P Value
White blood cell (×10³ cells/μL)	8.6 [6.1, 12.3][a]	8.9 [6.1, 13.1]	8.1 [6.4, 11.4]	7.9 [5.3, 10.9]	0.53
Hemoglobin (g/dL)	11.4 [10.5, 12.0]	11.5 [10.7, 12.2]	11.0 [10.2, 11.7]	11.1 [9.4, 12.2]	0.20
Platelets (×10³ cells/μL) (n = 107, 69, 15, 23)	182 [132, 231]	189 [133, 224]	217 [177, 264]	145 [95, 221]	0.026[c]
Absolute neutrophil count (×10³ cells/μL) (n = 104, 66, 16, 22)	6932 [4074, 9136]	6932 [4580, 9296]	7074 [4359, 9601]	6845 [3760, 8780]	0.77
Absolute lymphocyte count (×10³ cells/μL) (n = 104, 66, 16, 22)	1140 [625, 1766]	1266 [761, 2067]	892 [712, 1822]	610 [490, 980]	0.004[d]
Neutrophil to lymphocyte ratio (n = 104, 66, 16, 22)	6.0 [3.2, 11.5]	5.2 [3.1, 10.4]	8.9 [4.8, 13.0]	9.9 [5.3, 15.7]	0.022[e]
C-reactive protein (mg/dL)	14.2 [7.2, 19.7]	12.7 [6.3, 21.0]	16.7 [9.7, 19.3]	16.2 [8.9, 18.4]	0.82
Blood urea nitrogen (mg/dL) (n = 107, 68, 16, 23)	12 [9, 17])	11 [9, 17]	11 [9, 18]	13 [9, 22]	0.50
Creatinine (mg/dL) (n = 107, 68, 16, 23)	0.5 [0.4, 0.8]	0.5 [0.4, 0.8]	0.6 [0.4, 0.7]	0.5 [0.4, 0.8]	0.81
Albumin (g/dL) (n = 106, 68, 15, 23)	3.4 [3.0, 3.8]	3.4 [3.1, 3.9]	3.2 [2.8, 3.4]	3.3 [2.8, 3.8]	0.31
Alanine transaminase (unit/L) (n = 107, 69, 15, 23)	30 [17, 56]	32 [17, 58]	17 [15, 35]	37 [22, 52]	0.15
Lymphocytopenia[b]					
Lymphocytopenia (n = 104, 66, 16, 22)	49/104 (47%)	23/66 (35%)	9/16 (56%)	17/22 (77%)	0.002[f]
Lymphocytopenia and left ventricular dysfunction (n = 104, 66, 16, 22)	24/104 (23%)	14/66 (21%)	4/16 (25%)	6/22 (27%)	0.79

Data are summarized as number (percent) for categorical variables, and as median [interquartile range] for continuous variables. Comparisons are made across the three variant groups using either Fisher's exact test or the Kruskal-Wallis test

[a]Numbers in brackets represent interquartile ranges

[b] Lymphocytopenia defined as less than 1500 ×10³ cells/μL

[c]Applying a Bonferroni correction, platelets were higher durjng Delta than during Omicron

[d]Applying a Bonferroni correction, absolute lymphocyte count was higher during Alpha than during Omicron

[e]Applying a Bonferroni correction, neutrophil to lymphocyte ratio was lower during Alpha than during Omicron

[f]Applying a Bonferroni correction, lymphocytopenia was less frequent during Alpha than during Omicron

together, these data highlight the importance of investigating alternative diagnoses for MIS-C-like symptoms when the only evidence of recent COVID-19 is serologic [21].

Severity of illness at presentation in our series was generally similar among MIS-C cases occurring after exposure to the Alpha, Delta, and Omicron variants. Our experience differs from those in two earlier reports of population data, in which illness severity decreased over time [3, 22], but is similar to that of others report describing that MIS-C illness severity did not decline over time [4, 5]. The consistent severity of illness across time at our center may reflect referral bias at a tertiary medical center, with transfer of critically ill patients from outside emergency departments or hospitals. It could also potentially reflect a better ability to discriminate MIS-C from viral or other illnesses over time. This hypothesis is supported by the observation that fewer patients were admitted with MIS-C during Delta or Omicron eras compared to the Alpha era, despite widespread Omicron infections in the community [7]. Furthermore, almost all MIS-C cases in the Omicron era occurred when BA.1 was the predominant despite continued widespread COVID-19 in the community afterwards. It is possible that our findings could be related to misdiagnosis of MIS-C in an era of widespread antibody positivity and the absence of a pathognomonic test for MIS-C. However, we believe this is unlikely given that all cases were adjudicated both within our center and by our state Department of Public Health. Moreover, we did not rely upon antibodies alone to diagnose MIS-C, and many of the children in the Omicron cohort had had COVID-19 in the relevant period prior to MIS-C presentation.

Limitations of the study include the small sample size drawn from a single center. We did not have vaccination data for patients and the availability and prevalence of vaccination may have contributed to changes in MIS-C over time. We defined hypotension by clinician documentation rather than by blood pressures in order to include hypotension treated in outside emergency rooms, where records of blood pressure were sometimes incomplete. Because close exposure was defined as a household member with COVID-19 in the previous two months, our study did not account for exposure via community acquisition. We relied on classification of patients into variant waves by dates of admission using national data rather than genomic testing of SARS-CoV-2 samples from patients. Given the two-to-eight-week

period between COVID-19 and MIS-C, cases that occurred in the weeks surrounding periods of variant transitions could be misclassified. However, our sensitivity analysis using shifted cutoff dates did not affect the study's main conclusions. Timing of clinical presentation and therefore clinical features may have been influenced by unmeasured changes in behavior over time. Patients were adjudicated before the CDC released an updated MIS-C surveillance case definition effective January 2023 and not all patients in this study may meet the new criteria [23, 24].

In summary, our adjudicated single-center case series suggests that MIS-C in the Omicron era continues to be a critical illness with changing diagnostic challenges and incidence. Future multicenter studies should continue to refine diagnostic methods in light of evolving SARS-CoV-2 variants and population immunity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-023-04968-4.

Declarations

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