# Characteristics and Outcomes of Critically Ill Children With Multisystem Inflammatory Syndrome

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**OBJECTIVES:** To characterize the prevalence of pediatric critical illness from multisystem inflammatory syndrome in children (MIS-C) and to assess the influence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain on outcomes.

**DESIGN:** Retrospective cohort study.

**SETTING:** Database evaluation using the Virtual Pediatric Systems Database.

**PATIENTS:** All children with MIS-C admitted to the PICU in 115 contributing hospitals between January 1, 2020, and June 30, 2021.

**MEASUREMENTS AND MAIN RESULTS:** Of the 145,580 children admitted to the PICU during the study period, 1,338 children (0.9%) were admitted with MIS-C with the largest numbers of children admitted in quarter 1 (Q1) of 2021 ($n = 626$). The original SARS-CoV-2 viral strain and the D614G Strain were the predominant strains through 2020, with Alpha B.1.1.7 predominating in Q1 and quarter 2 (Q2) of 2021. Overall, the median PICU length of stay (LOS) was 2.7 days (25–75% interquartile range [IQR], 1.6–4.7 d) with a median hospital LOS of 6.6 days (25–75% IQR, 4.7–9.3 d); 15.2% received mechanical ventilation with a median duration of mechanical ventilation of 3.1 days (25–75% IQR, 1.9–5.8 d), and there were 11 hospital deaths. During the study period, there was a significant decrease in the median PICU and hospital LOS and a decrease in the frequency of mechanical ventilation, with the most significant decrease occurring between quarter 3 and quarter 4 (Q4) of 2020. Children admitted to a PICU from the general care floor or from another ICU/step-down unit had longer PICU LOS than those admitted directly from an emergency department.

**CONCLUSIONS:** Overall mortality from MIS-C was low, but the disease burden was high. There was a peak in MIS-C cases during Q1 of 2021, following a shift in viral strains in Q1 of 2021. However, an improvement in MIS-C outcomes starting in Q4 of 2020 suggests that viral strain was not the driving factor for outcomes in this population.

**KEY WORDS:** COVID-19; epidemiology; informatics; multisystem inflammatory syndrome in children; pediatric critical care; public health

Multisystem inflammatory syndrome in children (MIS-C) is a severe illness associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in children and young adults (1–7). It is potentially severe and life-threatening, with 14–74% of patients requiring admission to a PICU. First described in May 2020, MIS-C is characterized by a dysregulated host immune response following infection with the SARS-CoV-2 virus resulting in multisystem organ dysfunction (1, 5, 8, 9).

Several groups have described characteristics and outcomes of children with MIS-C (10–14). To date, there has not been a comprehensive longitudinal



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study of the characteristics and outcomes of critically ill children with MIS-C across the United States. Additionally, the relationship of its prevalence to strain variant remains unclear. We sought to characterize the prevalence and outcomes of MIS-C in critically ill children using a multicenter quality-controlled database and to assess the influence of SARS-CoV-2 strain on outcomes.

## METHODS

We conducted a retrospective analysis of prospectively collected data entered into the Virtual Pediatric Systems (VPS) database (VPS, LLC, Los Angeles, CA). VPS is a validated and quality controlled clinical database dedicated to standardized data sharing among PICUs (15). More than 100 centers located predominately in the United States and Canada participated and contributed patient data to the dataset. This dataset is used to track outcomes, measure quality, and conduct research into pediatric critical care. VPS neither endorsed nor restricted our interpretation of these data. This study was reviewed by the Institutional Review Board (IRB) of Connecticut Children's Medical Center (IRB no. 20-080) and determined to be non-human subject research.

Study inclusion criteria were children less than 18 years old with a primary diagnosis of MIS-C admitted to PICUs and entered into the VPS database from January 1, 2020 to June 30, 2021.

As stipulated by VPS, anonymized patient-level data were divided into quarters, without date of admission. Quarters are defined by VPS as January 1 to March 31 (quarter 1 [Q1]), April 1 to June 30 (quarter 2 [Q2]), July 1 to September 30 (quarter 3 [Q3]), and October 1 to December 31 (quarter 4 [Q4]). For each quarter, data were collected regarding demographics (age, gender), severity of illness (Pediatric Index of Mortality [PIM] scores) (16, 17), supportive treatments (mechanical ventilation, extracorporeal membrane oxygenation [ECMO]), and outcomes (i.e., PICU and hospital length of stay [LOS], mortality). LOS was defined as the difference between physical discharge and admission dates and times. Data regarding viral strain were obtained from the Centers for Disease Control and were population-based not patient-specific (18).

Statistics were performed using SAS software (SAS Institute Inc, Cary, NC). Median and interquartile ranges (IQRs) were calculated for continuous variables, and frequencies (%) were calculated for categorical variables. Quarters were compared using the Pearson's chi-square or Fisher exact test (when $n < 5$) *for* categorical data and the Kruskal-Wallis test for continuous data.

## RESULTS

The VPS registry had 145,580 children admitted to 115 PICUs between Q1 of 2020 and Q2 of 2021 with 1,338 children (0.9%) admitted with a primary diagnosis of MIS-C (**Table 1**). Only one patient was diagnosed with MIS-C in Q1 of 2020, whereas Q1 of 2021 had the most patients (626 cases; 2.7% of PICU admissions). Q1 of 2020 also coincided with the largest peak of COVID infections during the study period (18). The original SARS-CoV-2 viral strain and the D614G Strain were the predominant strains through 2020, with Alpha B.1.1.7 predominating in Q1 and Q2 of 2021 (18).

### Demographics

Overall the cohort population comprised 61% males. Children 6 to less than 12 years old accounted for the largest age group with 41.9% of MIS-C cases, whereas adolescents 12–18 years old comprised 34.4% of cases. Only two neonates were diagnosed with MIS-C throughout all quarters.

### Admission Data

The majority of patients (62.3%) with MIS-C were admitted to the PICU from an emergency department (ED), whereas 30.0% were transferred from the general care floor and 8.1% were admitted from another ICU/step-down unit. The probability of mortality at admission remained relatively low throughout the study period, with an overall median PIM2 score of 1.15 (IQR, 0.96–1.55).

### Outcomes

Overall, the median PICU LOS for patients with MIS-C was 2.7 days (IQR, 1.6–4.7 d), and the median hospital LOS was 6.6 days (IQR, 4.7–9.3 d) (Table 1). Both the median PICU and hospital LOS per quarter decreased over the study period, with a significant decrease occurring between Q3 and Q4 of 2020 (**Fig. 1**) ($p < 0.0001$ for both). Patients transferred to the ICU from the general care floor and from another

## TABLE 1.
### Characteristics and Outcomes of Multisystem Inflammatory Syndrome in Children Admissions Quarter[a]

| | Quarter 2 2020 (*N* = 76) | Quarter 3 2020 (*N* = 208) | Quarter 4 2020 (*N* = 272) | Quarter 1 2021 (*N* = 626) | Quarter 2 2021 (*N* = 155) | *p*[b] |
|---|---|---|---|---|---|---|
| Predominant severe acute respiratory syndrome coronavirus 2 Strain | Original and D614G strain | Original and D614G strain | Original and D614G strain | Alpha B.1.1.7 strain | Alpha B.1.1.7 strain | |
| Percent of total PICU admissions | 0.4% (76/20,224) | 0.9% (208/23,738) | 1.1% (272/23,896) | 2.7% (626/23,234) | 0.7% (155/21,301) | |
| Male gender, *n* (%) | 44 (57.9) | 129 (62.0) | 172 (63.2) | 377 (60.2) | 93 (60.0) | 0.88 |
| Age, *n* (%) | | | | | | |
| Neonate (birth to 29 d) | 0 (0) | 2 (1) | 0 (0) | 0 (0) | 0 (0) | 0.095 |
| Infant (29 d to < 2 yr) | 3 (4.0) | 18 (8.7) | 18 (6.6) | 24 (3.8) | 4 (2.6) | 0.03 |
| Child (2 to < 6 yr) | 10 (13.2) | 37 (17.8) | 59 (21.7) | 109 (17.4) | 33 (21.3) | 0.33 |
| Child (6 to < 12 yr) | 32 (42.1) | 88 (42.3) | 107 (39.3) | 280 (44.7) | 53 (34.2) | 0.16 |
| Adolescent (12 to < 18 yr) | 31 (40.8) | 63 (30.3) | 88 (32.4) | 213 (34.0) | 65 (41.9) | 0.12 |
| Postoperative admission, *n* (%) | 1 (1.3) | 7 (3.4) | 4 (1.5) | 8 (1.3) | 6 (3.9) | 0.12 |
| Admitted from, *n* (%) | | | | | | |
| Any general care floor | 20 (26.3) | 67 (32.7) | 82 (30.5) | 180 (29.3) | 40 (26.5) | 0.68 |
| Any emergency department | 46 (60.5) | 116 (55.6) | 170 (63.2) | 392 (63.8) | 96 (63.6) | 0.50 |
| Other ICU/step down unit | 10 (13.2) | 22 (10.7) | 17 (6.3) | 43 (7.0) | 15 (9.9) | 0.12 |
| Pediatric Index of Mortality 2 (median with IQR) | 1.18 (1.00–4.57) | 1.22 (0.95–3.90) | 1.17 (0.95–1.42) | 1.15 (0.96–1.48) | 1.09 (0.92–1.36) | 0.07 |
| PICU LOS (d), median (IQR) | 3.5 (2.2–6.6) | 3.7 (2.1–6.3) | 2.5 (1.6–4.6) | 2.5 (1.4-4.1) | 2.6 (1.5–4.9) | < 0.0001 |
| Hospital LOS (d), median (IQR) | 7.1 (4.8–9.7) | 7.8 (5.6–12.7) | 6.1 (4.4–8.8) | 6.4 (4.7-8.7) | 6.3 (4.6–9.2) | < 0.0001 |
| Mechanically ventilated, *n* (%) | 19 (25.0) | 50 (24.0) | 34 (12.5) | 82 (13.1) | 20 (12.9) | 0.0002 |
| Duration mechanically ventilated (d), median (IQR) | 2.6 (0.8–5.7) | 4.0 (2.4–7.0) | 3.0 (1.8–9.4) | 2.7 (1.5–5.1) | 3.1 (2.1–5.0) | 0.17 |
| Extracorporeal membrane oxygenation, *n* (%) | 1 (1.3) | 4 (1.9) | 3 (1.1) | 4 (0.6) | 1 (0.7) | 0.42 |
| Died during hospitalization, *n* (%) | 0 (0) | 2 (1.0) | 6 (2.2) | 2 (0.3) | 1 (0.7) | 0.07 |

IQR = interquartile range, LOS = length of stay.

[a]One child admitted in quarter 1 of 2020 not shown.

[b]$\chi^2$ or Fisher exact test was performed for categorical variables; Kruskal-Wallis test was performed for comparison of group medians.

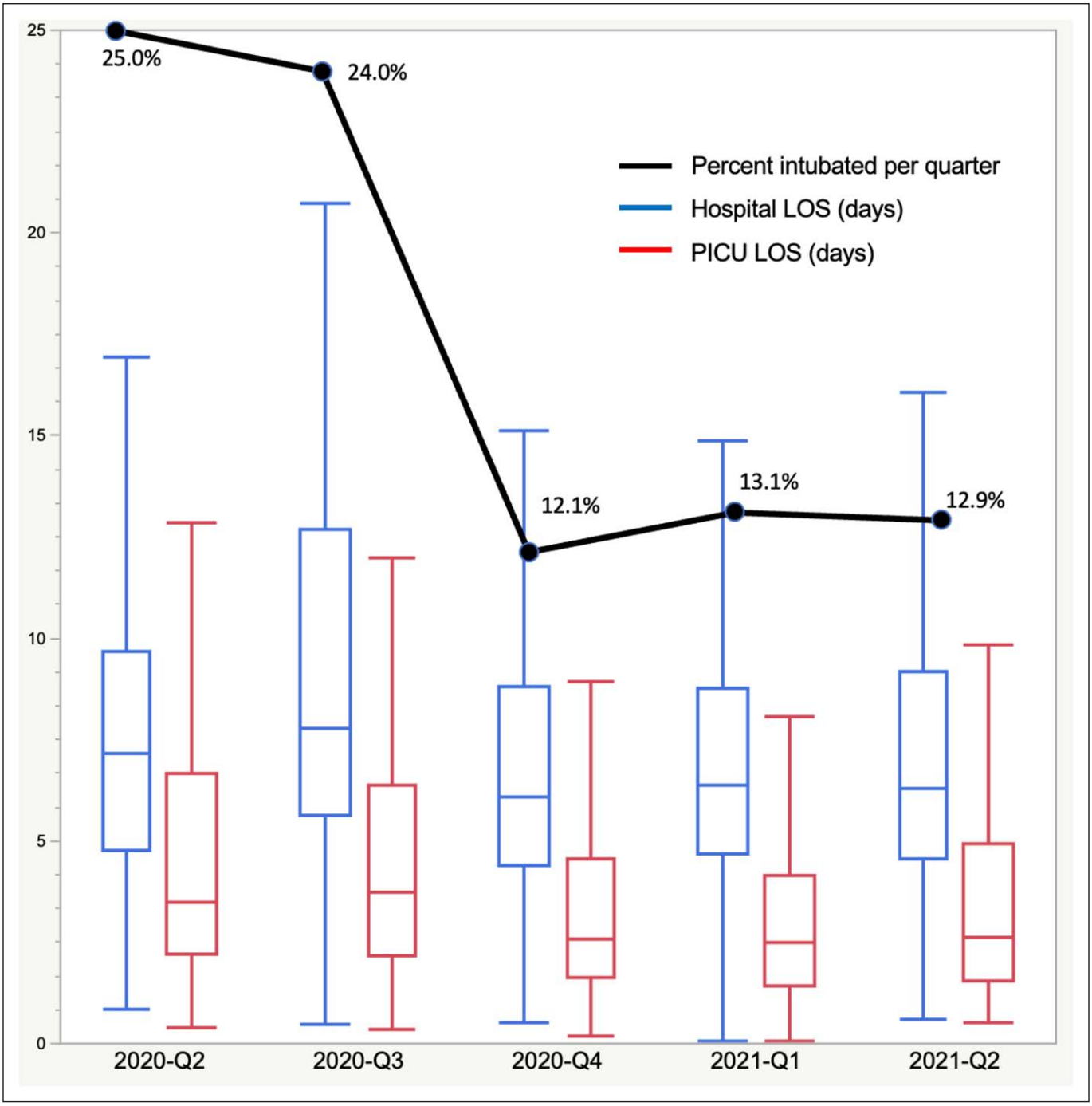


**Figure 1.** Outcomes of children with multisystem inflammatory syndrome in children by quarter. Data presented as median with 25–75% interquartile range and range or as frequency (%). LOS = length of stay, Q = quarter.

ICU/step-down unit had a longer median hospital LOS (7.6 d [IQR, 5.4–10.5 d, and 7.2 d [IQR, 5.1–13.1 d], respectively) compared with those admitted directly from an ED (median hospital LOS 5.9 d [IQR, 4.4–8.4 d]; $p < 0.0001$) (**Supplemental Table**, http://links.lww.com/PCC/C176). Children admitted from another ICU/step-down unit had longer ICU LOS than those admitted from the ED or general care floor (median PICU LOS 3.1 d [IQR, 1.8–6.7 d] vs 2.7 d [IQR, 1.6–4.6 d] and 2.7 d [1.4–4.5 d]; $p = 0.02$) (Supplemental Table, http://links.lww.com/PCC/C176).

Overall, 15.2% of MIS-C patients received mechanical ventilation for a median of 3.1 days (IQR, 1.9–5.8 d). The frequency of mechanical ventilation decreased over the study period, with a significant decrease occurring between Q3 and Q4 of 2020 ($p = 0.001$) (Fig. 1). The use

of ECMO remained low throughout all quarters with only 13 patients (1%) requiring this support. Hospital mortality was also low with 11 total deaths (0.8%).

## DISCUSSION

To our knowledge, this is the largest published cohort of critically ill MIS-C patients to date. Overall mortality from MIS-C was low, but the disease burden was high with a median hospital stay of almost a week, a median ICU LOS of almost 3 days, and more than 15% of children receiving mechanical ventilation. Over the course of the study, the frequency of mechanical ventilation decreased and both hospital and PICU LOS shortened.

There was a significant decrease in LOS and frequency of intubation between Q3 and Q4 of 2020. The driving factors for this decrease are unclear and may be due to an improvement in therapeutic interventions, improved recognition of the disease, availability of antibody testing, occurrence/recognition of milder disease over time, or a combination of these factors. The predominant viral strain changed in Q1 of 2021 (18), after the observed improvement in outcomes. Q1 of 2021 had the highest number of MIS-C patients, coinciding with a large peak of COVID infections in the United States, suggesting that either illness severity from MIS-C decreased with this strain or that there were improved therapeutic interventions. From May 2020 to early 2021, there was a rapid growth in the understanding of MIS-C and dissemination of that knowledge (10–14, 19, 20). This included the American College of Rheumatology consensus guidelines for the treatment of MIS-C published in June 2020 and modified in October 2020 (19). Given the timing of the different viral strains, an improved understanding of MIS-C is a more likely explanation for improved outcomes.

We observed that children admitted to the PICU from the general care floor had a longer hospital LOS but not PICU LOS when compared with children admitted from the ED. Unfortunately, the VPS does not contain data regarding treatments received. But, this difference suggests that once children are admitted to the PICU they do equally well, but that prompt determination of appropriate disposition can aid in providing definitive therapy.

Our study has several limitations due to its dataset and design. First, this was an observational study involving a retrospective analysis of a large dataset designed for quality-benchmarking, thus with a risk of inaccurate data entry. This is mitigated by the strict quality control measures employed by VPS decreasing the likelihood of data entry errors (15). Second, medication data are not available in the dataset, so we are unable to determine the association of therapeutic interventions and outcomes in this cohort. Third, given that we included data from 115 centers, our findings might not be representative of all PICUs in North America. However, the inclusion of centers from various regions with diverse characteristics likely allows our findings to be generalizable. Our data were also analyzed by quarter to maintain the anonymized nature of the dataset. Therefore, we were unable to conduct a more granular analysis for admission dates that might have a correlation between peaks of MIS-C in relation to the different strains of SARS-CoV-2. A lag between infection and onset of MIS-C may further confound relationships. Finally, VPS data availability precluded analysis of the Delta B.1.617.2 strain (July to December 2021 or Q3–Q4 of 2021) and Omicron B.1.1.529 strain (January 2022 to or Q1 of 2022), but these may provide an opportunity for future exploration.

## CONCLUSION

Although children admitted to the PICU with MIS-C had a low mortality, the hospitalization and illness burden was significant in these children. There was a peak in MIS-C cases during Q1 of 2021 which coincided with a peak in COVID infections in the United States and a shift in viral strains. However, an improvement in MIS-C outcomes starting prior to this shift in Q4 of 2020 suggests that viral strain was not the driving factor for outcomes in this population.

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