Severity and Incidence of Multisystem Inflammatory Syndrome in Children During 3 SARS-CoV-2 Pandemic Waves in Israel

Multisystem inflammatory syndrome in children (MIS-C) is a serious complication of SARS-CoV-2 infection. A previous study that described MIS-C cases in the first 3 waves of the COVID-19 pandemic found that the proportion of individuals with severe illness declined after the first wave. In Israel, the Omicron (B.1.1.529) variant started to spread in November 2021. We describe outcomes of MIS-C in a multicenter cohort and assessed incidence nationally during the Alpha, Delta, and Omicron variant waves.

Methods | To assess cardiac involvement and admission to the intensive care unit (ICU) in patients with MIS-C, a prospective study was conducted in 12 Israeli hospitals over a 16-week period of each pandemic wave. These participating institutions account for approximately 70% of the admissions to pediatric ICUs in Israel. Data of all patients with MIS-C younger than 18 years from the Alpha (December 20, 2020, to April 10, 2021), Delta (July 18, 2021, to November 13, 2021), and Omicron (November 21, 2021, to March 12, 2022) waves were prospectively collected. Vaccination status was determined by reviewing the SARS-CoV-2 digital vaccination record. The MIS-C definition was based on Centers for Disease Control and Prevention criteria. For purposes of incidence estimation, national data on SARS-CoV-2 infection and MIS-C were obtained from the Israel Ministry of Health SARS-CoV-2 data set and the MIS-C registry. The same 16-week periods for each wave were used for the MIS-C incidence estimation as for the assessment of outcomes. SARS-CoV-2 infections were confirmed using nasopharyngeal sample reverse transcriptase-polymerase chain reaction testing. Statistical analysis and calculation of incidence rate ratios (IRRs) were performed using StatsDirect statistical software, version 3.3.4 (StatsDirect Ltd). Statistical significance was defined as a 95% CI that did not include 1.

Results | In the 12 participating hospitals, 171 patients with a median (IQR) age of 8 (5-12) years were diagnosed with MIS-C; 59 during the Alpha wave, 79 during the Delta wave, and 33 during the Omicron wave. Ninety-four patients (55%) were males. All patients were treated with intravenous immunoglobulins and steroids. In 5 of 79 patients (6.3%) during the Delta wave and 5 of 33 (15.1%) during the Omicron wave, a second SARS-CoV-2 vaccine dose had been administered at least 2 weeks before hospital admission. None of the vaccinated patients were admitted to the ICU or required treatment with vasopressors.

Cardiac outcomes were more favorable during the Omicron wave (Table 1). Admission to the ICU occurred in 34 patients (57.6%) during the Alpha wave, 39 (49.4%) during Delta, and 7 (21.2%) during Omicron, and median hospital length of stay was 2 days shorter during Omicron than the Alpha and Delta waves. Vasopressors were used in 22% of patients during Alpha, 17.7% during Delta, and 6.0% during Omicron, and mechanical ventilation was used in 8.5% of patients during Alpha, 8.9% during Delta, and in no patients during Omicron. One patient died during the Delta wave.

Nationwide, in persons younger than 18 years, there were 188,800 SARS-CoV-2 infections and 103 patients with MIS-C during Alpha, 233,585 SARS-CoV-2 infections and 115 patients with MIS-C during Delta, and 946,779 SARS-CoV-2 infections and 36 patients with MIS-C during Omicron. MIS-C incidences per 100,000 persons younger than 18 years were 54.5 during Alpha, 49.2 during Delta, and 3.8 during Omicron. There was a higher incidence of MIS-C among patients during the Alpha wave (IRR, 14.34 [95% CI, 9.81-20.96]) and Delta wave (IRR, 12.94 [95% CI, 8.90-18.81]) compared with the Omicron wave (Table 2).

Discussion | This study suggests that MIS-C during the Omicron wave was less severe than during the Alpha or Delta waves of the COVID-19 pandemic. Possible explanations include the Omicron variant itself, previous infection with SARS-CoV-2, vaccination against SARS-CoV-2, and improvement in treatment over time. In addition, the incidence rate of MIS-C during the Omicron wave was lower than during the Delta and Alpha waves. A 2022 study from South Africa on the Omicron wave reported no cases of MIS-C, a finding that corroborates these results. Limitations of the study include the small number of patients in...
The prospective cohort and the single-country data. Because MIS-C is a late-onset phenomenon of SARS-CoV-2 infection, cases that appeared after the 16-week period of each wave were not included.

Nital Levy, MD
Jordanna H. Koppel, MD
Or Kaplan, MD
Hadas Yechiam, MD
Keren Shahar-Nissan, MD
Naama Kuchinski Cohen, MD
Itai Shavit, MD

Author Affiliations: Pediatric Emergency Department, Rambam Health Care Campus, Haifa, Israel (Levy, Shavit); Pediatric Emergency Department, Sheba Medical Center, Tel Hashomer, Israel (Koppel); Pediatric Emergency Department, Soroka Medical Center, Beer Sheva, Israel (Kaplan); Pediatric Emergency Department, Meir Medical Center, Kfar Saba, Israel (Yechiam); Emergency Department, Schneider Children’s Medical Center, Petah Tikva, Israel (Shahar-Nissan); Pediatric Emergency Department, Hillel Yaffe Medical Center, Hadera, Israel (Kuchinski Cohen).

Accepted for Publication: April 27, 2022.

Published Online: May 19, 2022. doi:10.1001/jama.2022.8025

Corresponding Author: Itai Shavit, MD, PO Box 274, Kibbutz Maayan Tzvi 3080500, Israel (itai@pem-database.org).

Author Contributions: Drs Levy and Shavit had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest Disclosures: None reported.

Additional Contributions: In addition to the individuals recognized previously, we acknowledge the following individuals for their assistance with this study: Nachshon Buchshtav, MD (Pediatric Emergency Department, HaEmek Medical Center), for data collection; Giora Weiser, MD (Pediatric Emergency Department, Carmel Medical Center), for data collection and data assistance; Zeev Schnapp, MD (Pediatric Emergency Department, Carmel Medical Center), for data collection; and Irena Chistyakov, MD (Pediatric Emergency Department, Bnai Zion Medical Center), for data collection and data assistance. None of these individuals received compensation for their roles in the study.


---

Table 1. Outcomes of Patients With MIS-C in 12 Israeli Hospitals During the Alpha, Delta, and Omicron Waves

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alpha wave* (n = 59)</th>
<th>Delta wave* (n = 79)</th>
<th>Omicron wave* (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP level, median (IQR), pg/mL</td>
<td>2961 (931-15 900)</td>
<td>2275 (799-4919)</td>
<td>1068 (435-5933)</td>
</tr>
<tr>
<td>Troponin level, median (IQR), ng/L</td>
<td>10 (5-113)</td>
<td>23 (13-57)</td>
<td>55 (25-157)</td>
</tr>
<tr>
<td>Reduced left ventricular function, No. (%)b</td>
<td>5 (8.5)</td>
<td>6 (7.6)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Length of stay and admission to ICU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay, median (IQR), d</td>
<td>6 (5-8)</td>
<td>6 (5-8.5)</td>
<td>4 (3-6)</td>
</tr>
<tr>
<td>ICU length of stay, median (IQR), d</td>
<td>3 (2-6)</td>
<td>4 (2-6)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>ICU admission, No. (%)b</td>
<td>34 (57.6)</td>
<td>39 (49.4)</td>
<td>7 (21.2)</td>
</tr>
<tr>
<td>ICU treatment, No. (%)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressors</td>
<td>13 (22.0)</td>
<td>14 (17.7)</td>
<td>2 (6.0)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>5 (8.5)</td>
<td>7 (8.9)</td>
<td>0</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>0</td>
<td>2 (2.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide.

Table 2. Nationwide Data on the Incidence of MIS-C During the Alpha, Delta, and Omicron Waves in Israel

<table>
<thead>
<tr>
<th>Pandemic wave dataa</th>
<th>Alpha</th>
<th>Delta</th>
<th>Omicron</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIS-C cases, No. (%)b</td>
<td>103 (40.5)</td>
<td>115 (45.3)</td>
<td>36 (14.2)</td>
<td>254</td>
</tr>
<tr>
<td>SARS-CoV-2 infections in persons younger than 18 y, No. c</td>
<td>188 800</td>
<td>233 585</td>
<td>946 779</td>
<td>1 369 164</td>
</tr>
<tr>
<td>MIS-C incidence ratea</td>
<td>54.5</td>
<td>49.2</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>MIS-C incidence rate ratio (95% CI) e</td>
<td>14.34 (9.81-20.96)</td>
<td>12.94 (8.90-18.81)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide.

a Each wave was a 16-week period: Alpha, December 20, 2020, to April 10, 2021; Delta, July 18, 2021, to November 13, 2021; and Omicron, November 21, 2021, to March 12, 2022.

b Cases of multisystem inflammatory syndrome in children (MIS-C) were limited to patients aged 0 to 18 years.

c According to the Israel Ministry of Health SARS-CoV-2 data set.

---

Concept and design: Levy, Kaplan, Shavit. Acquisition, analysis, or interpretation of data: Levy, Koppel, Yechiam, Shahar-Nissan, Kuchinski Cohen. Drafting of the manuscript: Levy, Kaplan, Yechiam, Kuchinski Cohen, Shavit. Critical revision of the manuscript for important intellectual content: Levy, Koppel, Kaplan, Shahar-Nissan, Kuchinski Cohen. Statistical analysis: Shavit. Administrative, technical, or material support: Koppel, Kaplan, Yechiam, Kuchinski Cohen. Supervision: Levy, Shavit.

© 2022 American Medical Association. All rights reserved.
Characteristics and Outcomes of Patients With COVID-19–Associated ARDS Who Underwent Lung Transplant

To the Editor A recent study reported impressive outcomes in 30 patients who underwent lung transplant for COVID-19–associated acute respiratory distress syndrome (ARDS). However, we wonder whether some patients in this cohort may not have needed a lung transplant if given more time to recover.

Despite its lifesaving potential, lung transplant is a life-limiting procedure and should be considered only for those with unquestionably irreversible lung damage. The authors reported referring patients for transplant after a multidisciplinary team determined “no longitudinal evidence of lung recovery after at least 4 to 6 weeks had elapsed from the onset of COVID-19–associated ARDS.” We question how the authors established irreversibility of parenchymal damage, especially in patients who received a lung transplant within 2 to 3 months after the onset of COVID-19, which represented nearly a third of the cohort as shown in eTable 2 of the article’s Supplement.

To our knowledge, there is a lack of evidence about how to predict the potential of parenchymal recovery in COVID-19–associated ARDS. Weighing the likelihood of death against the odds of improvement in these patients who have a high mortality rate is extremely challenging. Still, we caution against proceeding with lung transplant too early in the disease course without allowing sufficient time for lung recovery, recognizing that the alternative of delaying may be costly.

Because donor lungs remain an extremely limited resource, patients continue to develop COVID-19–associated ARDS, increasing the gap between the number of patients who need organs and the number of organs available. It is thus imperative to pursue all alternative avenues to recovery, possibly for longer duration than has been typically used. Recently published high-quality studies support the use of extracorporeal membrane oxygenation (ECMO) for ARDS, and large multicenter studies have reported good outcomes with the use of ECMO for COVID-19–associated ARDS. In light of this evidence, prolonged ECMO support, extending past 28 days, may be necessary to bridge some patients with COVID-19–associated ARDS to recovery, instead of bridging to lung transplant.

Darya Rudym, MD
Stephanie H. Chang, MD
Luis F. Angel, MD

Author Affiliations: Department of Medicine, New York University Langone Health, New York, New York (Rudym, Angel); Department of Cardiothoracic Surgery, New York University Langone Health, New York, New York (Chang).

In Reply Institutional and national cohort studies have reported the success of lung transplant for COVID-19–associated ARDS. However, given the unpredictable trajectory of patients with COVID-19–associated ARDS and the lack of clinically available biomarkers of permanent lung injury, referral for lung transplant requires careful evaluation of pulmonary physiology, radiographic and histologic changes, medical course, and treatment response. Furthermore, lung transplant referral should only be considered after sufficient time has passed from the onset of ARDS and after longitudinal multidisciplinary evaluation indicates that lung recovery or successful liberation from life support is unlikely.

Although the lungs can recover after an extended duration of ECMO, the in-hospital mortality of patients with COVID-19–associated ARDS requiring ECMO remains high, at 40% to 50%. Additional analysis of our study cohort revealed that the probability of weaning from ECMO and surviving to hospital discharge decreased with increasing duration of extracorporeal support. For patients who required ECMO support for 1 month, survival to hospital discharge was less than 10%, and for those receiving ECMO for 40 days, survival decreased to 5%. Furthermore, patients who successfully underwent weaning from ECMO after 28 days of ECMO support experienced greater postdischarge mortality compared with those supported with ECMO for less than 28 days (Figure).

ECMO is expensive, and extended duration of ECMO use generates extremely high costs, requires substantial intensive care unit resources, and may cause moral distress in treating clinicians and nursing staff. Therefore, the potential for lung recovery and the risks of premature transplant should be weighed carefully against the risk of increased mortality and high resource utilization associated with longer duration of critical illness and ECMO use. We recommend that optimal medical support be continued as long as lung recovery is