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Note

# Comparison of the clinical characteristics and outcomes of COVID-19 in children before and after the emergence of Delta variant of concern in Japan

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ABSTRACT

Delta variant of concern (VOC) is the current predominant severe acute respiratory coronavirus type 2 strain causing coronavirus disease 2019 (COVID-19); however, information regarding the impact of the Delta VOC on clinical features and outcomes in pediatric patients with COVID-19 is limited. We conducted a retrospective observational study using the data of patients <18 years of age in COVIREGI-JP, the COVID-19 registry in Japan. The patients were divided into two groups according to the timing of enrollment in the registry (pre-Delta VOC era, October 2020 to May 2021; and Delta VOC era, August to October 2021), and the clinical characteristics and outcomes were compared between the two groups. During the study period, 950 and 349 pediatric patients were registered in the pre-Delta VOC and Delta VOC eras, respectively. The median patient age was younger and the proportion of patients with underlying diseases was higher in the Delta VOC era than that in the pre-Delta VOC era (10.0 vs 7.0 years, $P < 0.001$, and 7.4% [n = 70] vs. 12.6% [n = 44], $P = 0.004$, respectively). Significantly more patients were admitted to the intensive care unit in the Delta VOC era than in the pre-Delta VOC era (1.4% [n = 5] vs. 0.1% [n = 1], $P = 0.006$), but no patient in either group died or required mechanical ventilation or extracorporeal membrane oxygenation throughout the study period, suggesting that the overall outcomes in children with COVID-19 remained favorable even in the Delta VOC era in Japan.

Severe acute respiratory coronavirus type 2 (SARS-CoV-2) is a single-stranded RNA virus that causes coronavirus disease 2019 (COVID-19). Compared with DNA viruses, RNA viruses are more prone to the accumulation of mutations during replication [1], as evidenced by the recent emergence of numerous mutant variants of SARS-CoV-2 [2]. The Delta variant (Phylogenetic Assignment of Named Global Outbreak lineage B.1.617.2 and AY) is a major, highly contagious SARS-CoV-2 variant that may be associated with more severe disease [3] and has therefore been designated as a variant of concern (VOC) by the World Health Organization [2]. The Delta VOC was initially identified in India at time of December 2020 and is currently the most prevalent variant strain worldwide [4].

In Japan, the proportion of patients infected with the Delta VOC has been increasing since May 2021, rapidly reaching 80% or more around August 2021 [5]. Thus far in Japan, COVID-19 has often been asymptomatic or mild in children, with good clinical outcomes [6]. However, information regarding the impact of the Delta VOC on the clinical features and outcomes of pediatric COVID-19 is limited. Therefore, we investigated the clinical characteristics and outcomes of COVID-19 in children before and after the emergence of the Delta VOC.

We conducted a retrospective observational study using the data from COVIREGI-JP, the nationwide COVID-19 registry in Japan. The details of COVIREGI-JP were previously described [7]. Briefly, hospitalized patients diagnosed with COVID-19 based on nucleic acid amplification or rapid antigen test for SARS-CoV-2 were registered in COVIREGI-JP. As of November 2021, more than 700 institutions across Japan have been participating in the registry and more than 50,000 COVID-19 patients have been enrolled.

In the present study, patients aged <18 years were divided into two groups according to the timing of registry enrollment: pre-Delta VOC

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**Abbreviations**

| | |
|---|---|
| ICU | Intensive care unit |
| VOC | Variant of concern |

era, October 2020 to May 2021; and Delta VOC era, August to October 2021. Those enrolled in the registry between June 2021 and July 2021 were excluded, because the number of COVID-19 cases due to the Delta VOC was still increasing in Japan during that period.

Data on age, sex, underlying diseases, COVID-19 exposure history before admission, signs and symptoms, treatment, length of hospital stay, and outcomes were extracted from the registry. The information on Delta VOC positivity was not available for any of the patients. Categorical and continuous variables were described as numbers with percentages and medians with interquartile ranges (IQRs), respectively. The clinical characteristics and outcomes between the pre-Delta VOC era and Delta VOC era groups were compared using Fisher's exact and the Mann–Whitney U tests for categorical and continuous variables, respectively. A two-sided P value of $<0.05$ was considered to indicate statistical significance. The R statistical software version 4.0.5. was used for all statistical analyses.

The present study was approved by the Ethics Review Committees of the National Center for Global Health and Medicine and the National Center for Child Health and Development (NCGM-G-003494-0 and NCCHD-2020-313).

During the study reference period, 950 and 349 pediatric patients from 176 institutions were registered in the pre-Delta and Delta VOC eras, respectively. The characteristics of patients in these two groups are summarized in Table 1. Briefly, the median patient age was younger and the proportion of patients with underlying diseases was higher in the Delta VOC era compared with the pre-Delta VOC era (10.0 vs 7.0 years, $P < 0.001$, and 7.4% [n = 70] vs. 12.6% [n = 44], $P = 0.004$, respectively). In the Delta VOC era, the most predominant underlying disease was bronchial asthma, followed by obesity. During the study period, 281 (21.6%) of the pediatric patients registered in the database were asymptomatic; however, the number of asymptomatic patients was significantly lower in the Delta VOC era than that in the pre-Delta VOC era (36 [10.3%] vs. 245 [25.8%] $P < 0.001$).

Table 2 summarizes the comparison of COVID-19 severity and outcomes between the two study periods. There were no patient deaths and no patient required mechanical ventilation or extracorporeal membrane oxygenation throughout the study period. However, the number of patients admitted to the intensive care unit (ICU) was significantly higher in the Delta VOC era than in the pre-Delta VOC era (1.4% [ n = 5] vs.

**Table 2**
Comparison of severity and outcomes between the Pre-Delta VOC and Delta VOC periods.

| Variables | Total | Pre-Delta VOC era | Delta VOC era | *P* value |
|---|---|---|---|---|
| **Case number** | 1299 | 950 | 349 | |
| **Noninvasive oxygen support (nasal cannula, face mask, reservoir mask, high-flow oxygen device)** | 31 (2.4) | 20 (2.1) | 11 (3.2) | 0.305 |
| **Invasive mechanical ventilation/ECMO** | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |
| **ICU admission** | 6 (0.5) | 1 (0.1) | 5 (1.4) | 0.006 |
| **Length of hospital stay (days), median (IQR)** | 7.0 (5.0–9.0) | 8.0 (5.0–9.0) | 7.0 (5.0–9.0) | 0.031 |
| **Death** | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; NA, not applicable; VOC, variant of concern.

**Table 1**
Background characteristics of the study cohort.

| Variables | Number of cases | Subcategory | Total | Pre-Delta VOC era | Delta VOC era | *P* value |
|---|---|---|---|---|---|---|
| **Case number** | 1299 | | 1299 | 950 | 349 | |
| **Age (years), median (IQR)** | 1299 | | 9.0 (3.0–14.0) | 10.0 (4.0–15.0) | 7.0 (2.0–13.0) | <0.001 |
| **Age category, number (%)** | 1299 | 0 to <3 month | 25 (1.9) | 11 (1.2) | 14 (4.0) | <0.001 |
| | | 3 to <24 month | 202 (15.6) | 140 (14.7) | 62 (17.8) | |
| | | 2 to <6 years | 228 (17.6) | 156 (16.4) | 72 (20.6) | |
| | | 6 to <13 years | 382 (29.4) | 280 (29.5) | 102 (29.2) | |
| | | ≥13 years | 462 (35.6) | 363 (38.2) | 99 (28.4) | |
| **Male sex, number (%)** | 1299 | Male | 720 (55.4) | 529 (55.7) | 191 (54.7) | 0.801 |
| **Body mass index, median (IQR)** | 1051 | | 18.1 (16.0–20.8) | 18.4 (16.0–20.8) | 17.7 (15.9–20.4) | 0.090 |
| **Underlying disease*, number (%)** | 1299 | Any underlying disease | 114 (8.8) | 70 (7.4) | 44 (12.6) | 0.004 |
| | | Bronchial asthma | 58 (4.5) | 39 (4.1) | 19 (5.4) | 0.292 |
| | | Obesity | 17 (1.3) | 9 (0.9) | 8 (2.3) | 0.093 |
| | | Congenital heart anomaly | 16 (1.2) | 11 (1.2) | 5 (1.4) | 0.777 |
| | | Congenital anomaly or chromosomal abnormality | 8 (0.6) | 6 (0.6) | 2 (0.6) | 1.0 |
| | | Diabetes without complication | 7 (0.5) | 4 (0.4) | 3 (0.9) | 0.394 |
| | | Hypertension | 5 (0.4) | 3 (0.3) | 2 (0.6) | 0.615 |
| | | Others[#] | 16 (1.2) | 9 (0.9) | 7 (2.0) | 0.154 |
| **Immunosuppressive condition, number (%)** | 1299 | | 8 (0.6) | 5 (0.5) | 3 (0.9) | 0.450 |
| **Exposure within 14 days prior to admission** | 1280 | Travel abroad | 10 (0.8) | 10 (1.1) | 0 (0.0) | 0.004 |
| | 1284 | Close contact with COVID-19 cases | 1069 (83.3) | 783 (83.6) | 286 (82.4) | 0.202 |
| | 1299 | Family | 826 (63.6) | 597 (62.8) | 229 (65.6) | 0.363 |
| | | Educational facility | 181 (13.9) | 141 (14.8) | 40 (11.5) | 0.125 |
| | | Nonfamily roommates | 15 (1.2) | 13 (1.4) | 2 (0.6) | 0.379 |
| | | Workplace | 7 (0.5) | 6 (0.6) | 1 (0.3) | 0.682 |
| | | Healthcare facility | 5 (0.4) | 3 (0.3) | 2 (0.6) | 0.615 |
| | | Others | 51 (3.9) | 37 (3.9) | 14 (4.0) | 0.874 |
| **Days of hospitalization from symptom onset, median (IQR)** | 1011 | | 3.0 (1.0–4.0) | 3.0 (1.0–5.0) | 3.0 (1.0–4.0) | 0.981 |
| **Number of SARS-CoV-2-vaccinated patients** | 349 | | 4 (1.1) | 0 (NA) | 4 (1.1) | 1.0 |
| **Number of asymptomatic patients** | 1299 | | 281 (21.6) | 245 (25.8) | 36 (10.3) | <0.001 |

SARS-CoV-2, severe acute respiratory coronavirus type 2; VOC, variant of concern; IQR, interquartile range; NA, not applicable.

0.1% [n = 1], $P = 0.006$) and included two patients with bronchial asthma and one patient with obesity. To adjust the patient background in the two periods, we performed the same analysis for only symptomatic patients (Supplemental Table 1). The results were similar to those of the whole population, in that the number of patients admitted to the ICU was significantly higher in the Delta VOC era than that in the pre-Delta VOC era (1.6% [n = 5] vs. 0.1% [n = 1], $P = 0.012$).

The present retrospective registry data study revealed that the ICU admission rate in the Delta VOC era was higher and that half of the ICU admitted patients had underlying diseases.

Several reports suggested that the Delta VOC might be associated with more severe COVID-19 compared to the other variants, based on the higher COVID-19 admission rate observed in the Delta VOC era compared with the era of Alpha variant under monitoring (VUM), the formerly dominant variant (hazard ratio, 1.85–2.26) [3,8]. The epidemiological analysis of COVID-19 in children between August 2020 and August 2021 by the Centers for Disease Control and Prevention revealed that the hospital admission of pediatric patients with COVID-19 increased after the Delta VOC became the predominant variant strain [9]. The percentage of hospitalizations resulting in mechanical ventilation was 0%–3% during the current study period and did not dramatically change after the emergence of the Delta VOC. In the present study, the ICU admission rate was higher in the Delta VOC era than in the pre-Delta VOC era. The hospitalization rate of COVID-19 during the Delta VOC era was relatively low despite the increase in the total number of patients [10], raising the possibility that more severe patients were admitted, which might have influenced the high ICU admission rate detected in the Delta VOC era. Therefore, whether the Delta VOC is associated with severe COVID-19 in children remains unclear. On the other hand, the absolute number of pediatric patients admitted to the ICU during the Delta VOC era was high, indicating the importance of minimizing the total number of pediatric patients with COVID-19.

In addition to different SARS-CoV-2 strains, underlying diseases might also be associated with COVID-19 severity. COVID-19 might be more severe in patients with underlying diseases than in those without underlying diseases [11]. The present study revealed that the proportion of patients with any underlying disease was higher in the Delta VOC era and 3/6 (50%) of the pediatric patients admitted to the ICU had underlying diseases. These findings might be associated with the higher ICU admission rate observed in the Delta VOC era and might indicate that the relatively high benefit of SARS-CoV-2 immunization in children with underlying diseases.

The outcomes of COVID-19 in children in Japan were still favorable. No patient death was identified in the registry. According to national reports, there have been no deaths in children under the age of 10 years, and only three deaths have been reported among teenagers in Japan [12]. On the other hand, many severe cases and deaths in children have been reported overseas. In the United States, for example, 790 deaths of COVID-19 patients aged 0–18 years have been reported [13]. There are several hypotheses for the better outcomes of pediatric COVID in Japan. It is known that multisystem inflammatory syndrome (MIS-C), a common cause of death in COVID-19 patients, is less common in Asians [14]. This suggests that some genetic factors may be associated with the severity of COVID-19 in children. In addition, obesity, which is a risk factor for severe COVID-19, may be less prevalent in Japan. In fact, the percentage of obese patients in our cohort was only 1.3%, although in a study conducted in the US, 31.5% of hospitalized pediatric patients with COVID-19 were obese [15]. However, these factors alone do not explain all the results, and further studies are required to provide more definitive conclusions.

The present study has several limitations. First, information on the presence of Delta VOC was not available in all patients; therefore, the impact of the Delta VOC on COVID-19 outcomes in children could not be directly assessed. However, according to genomic weekly lineage Japan reported by the National Institute of Infectious Diseases, the Delta VOC rates in Japan were 0.5% and 93.6% in the pre-Delta VOC and the Delta VOC eras, respectively, during the present study period [5]. Unfortunately, genomic surveillance was only performed for approximately one-tenth of the newly diagnosed cases during the study reference period; therefore, our results may not be entirely representative of the overall picture. Second, the impact of other VOCs was not assessed. Data from the National Institution of Infectious Diseases revealed that only 0.04% and 0.15% of the Beta and Gamma VOCs and 50.8% of the Alfa VUM were detected in the pre-Delta era [5]. Therefore, we believe that the effect of other VOCs could be ignored. Third, we did not have information regarding the indications for hospitalization. In the early stage of the epidemic, all patients required hospitalization. Thereafter, patients had the option of hotel or home isolation. Therefore, the population of hospitalized patients in the pre-Delta and Delta eras may differ, which makes it difficult to directly compare these two periods. Fourth, COVIREGI-JP is a voluntary registry and not all patients with COVID-19 in Japan are enrolled in this registry. There is no data regarding the total number of hospitalized pediatric patients in Japan; however, approximately 220,000 COVID-19 patients under the age of 20 years were diagnosed during the study reference period [12]. Therefore, our findings may not be a complete representation of the COVID-19 pandemic in Japan.

In conclusion, the ICU admission rate in the registry was higher in the Delta VOC era than in the pre-Delta VOC era among pediatric patients with COVID-19 in Japan. Nevertheless, the outcomes remained favorable in the Delta VOC era among these patients. Further large-scale studies are necessary to directly compare outcomes between patients with and without Delta VOC and to more precisely elucidate the impact of the Delta VOC on COVID-19 outcomes in children.

## Authorship statement

All authors meet the ICMJE authorship criteria. KS contributed to conceptualizing and designing the study and drafted the manuscript. TA, ST, NM, YA, SS, and NI contributed to data collection, statistical analysis, and revising of the manuscript. TF contributed to the conceptualization and design of the study and revised the manuscript. NO contributed to the conceptualization and design of the study, revised the manuscript, and supervised the study. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.01.009.

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