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Hospital burden and characteristics of pediatric COVID-19 based on a multicenter collaborative retrospective study in Japan

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ABSTRACT

Objectives: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant emergence preceded a wave of pediatric coronavirus disease 2019 (COVID-19) cases, putting considerable strain on hospitals across Japan. Our study evaluated the pediatric disease burden of COVID-19 in pediatric hospitals.
Methods: This retrospective study evaluated all pediatric patients (defined as aged < 21 years) hospitalized with SARS-CoV-2 infection, or as close contacts, at four children's hospitals, between January 1 and May 31, 2022. Clinical characteristics, reasons for admission, and outcome data were analyzed.
Results: In total, 492 patients (median age 3.0 years; male 58.7%) were included over the study period. Of these, 232 (47.2%) patients had at least one underlying disease. Asymptomatic and mild diseases were common during the study period (n = 451, 91.7%). Social reasons for hospitalization (including a lack of family support at home) accounted for 36.8% (n = 181) of inpatients. The median length of stay was 4.0 days. Fever was the most common symptom (n = 273, 55.5%), followed by upper respiratory (n = 77, 15.7%) and neurological (n = 60, 12.2%) symptoms. Overall, 34 (6.9%) children required invasive mechanical ventilation, 51 (10.4%) were admitted to the pediatric intensive care unit, and two (0.4%) died. COVID-19 vaccination rate was low (n =14/200, 7.0%).
Conclusions: The disease burden during the Omicron-predominant period was attributable to asymptomatic and mild infections, and some patients were hospitalized for social reasons. To maintain a medical care system for critically ill patients, each medical facility must play a role according to its function.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide since 2019 [1,2]. Since the first confirmed case of COVID-19 in Japan on January 16, 2020, Japan has experienced six waves of the COVID-19 pandemic, which occurred over the following periods: January 26 to May 31, 2020; July to September 2020; October 2020; May to June 2021; July to September 2021; and January 2022. Following the emergence of the Omicron variant in Japan in January 2022, large numbers of pediatric COVID-19 cases were newly diagnosed [3,4]. Young patients with COVID-19 usually have mild disease; however, information on the hospital burden and characteristics of pediatric COVID-19 is limited.

Definitions of severe disease in pediatric patients vary, but in Japan they generally reflect respiratory symptoms and a requirement for respiratory support or oxygen saturation [5]. Since February 1, 2020, COVID-19 has been classified as a legally designated infectious disease in Japan (under the Infectious Diseases Act) [6]. When the first wave began, the indication for hospitalization was, in principle, for all COVID-19 patients. Subsequently, following the nationwide spread of the infection, accommodation and home care were made available for mildly ill patients who were not at risk of serious illness. After the second wave, hospitalization was generally indicated for patients with moderate to severe disease. On the other hand, children are often admitted to hospital for reasons unrelated to COVID-19, and may be found to have asymptomatic or mild symptomatic infections.

Isolation periods were initially established as 14 days for symptomatic patients, 12.5 days for patients with no symptoms, and 14 days for close contacts. However, as knowledge of the period of communicability improved, the isolation period was reduced to 10 days for patients with mild/no symptoms, 14 days for patients with severe symptoms, and 7 days for close contacts during the Omicron-predominant period.

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The associated outbreak of pediatric COVID-19 put considerable strain on many hospitals across Japan. Even the children's hospitals, which are specialized medical centers for children, were functioning near capacity as a result of COVID-19 patients.

Our hypothesis was that there was an increased disease burden affecting hospital functions. The aim of our study was therefore to clarify the impact of these conditions by evaluating the disease burden of pediatric COVID-19 in our children's hospitals.

Methods

Study design

This retrospective study included all patients with COVID-19, or their close contacts, hospitalized between January 1 and May 31, 2022. The study was approved by our institutional review board (no. R4-63). Informed consent was obtained from parents using the opt-out method.

Setting

This study was conducted in children's hospitals with a total catchment area encompassing 3.0 million children across four prefectures in Japan [7]. During the study period, the region was heavily affected by COVID-19, resulting in restrictions against new hospitalizations and the postponement of scheduled surgeries in our children's hospitals. The study period was selected to coincide with the Omicron variant outbreak in Japan [4].

Participants

The inclusion criteria were as follows: age < 21 years (the upper age limit for patients treated by pediatricians, as recommended by the Japanese Society of Pediatrics) [8]; positive SARS-CoV-2 test result by polymerase chain reaction (PCR) or antigen test, or a close contact of an infected patient. The exclusion criterion was an absence of documented positive SARS-CoV-2 PCR or antigen assay results, or of documentation confirming false-positive SARS-CoV-2 PCR or antigen test results.

Variables

Patients were categorized into the following groups at discharge: those with a positive SARS-CoV-2 result by PCR or antigen test, and those who were close contacts. Underlying diseases were categorized as comorbidities (according to the high-risk group defined by the Japanese Society of Pediatrics) [8], and included chronic respiratory disease, chronic heart disease, chronic renal disease, neurological or neuromuscular disease, hematologic or malignant disease, metabolic or endocrine disease, collagen or autoimmune disease, gastrointestinal or liver disease, immunodeficiency disease or use of immunosuppressive agents, and other conditions such as obesity, premature birth, and anorexia. Hospitalization was defined based on a principal clinical diagnosis necessitating hospital admission. The indication for hospitalization due to social reasons was defined as hospitalization not due to medical indications for COVID-19, but due to human resource and material problems, including social vulnerability either at home, in welfare facilities, or in medical facilities. Social reasons were categorized as a lack of family support at home, difficulty due to isolation at public assistance facilities, or difficulty during hospitalization at other primary or secondary medical facilities due to COVID-19 diagnosis. Disease severity was categorized as asymptomatic, mildly symptomatic, moderately symptomatic, or severe (according to the category of severity defined by 'Clinical management of patients with COVID-19: a guide for front-line healthcare workers in Japan') [5]. Asymptomatic disease was defined as the absence of: documented fever, respiratory symptoms (cough, shortness of breath, or difficulty breathing); gastrointestinal symptoms (nausea, vomiting, or abdominal pain); or neurological symptoms (seizure, alteration of consciousness, dysgeusia, or olfactory dysfunction) before or during hospitalization. Patients who were admitted with these symptoms but who had a clearly documented alternative reason, were also deemed to have an asymptomatic diagnosis. Mild disease was defined as occurrence of fever and respiratory, gastrointestinal, or neurological symptoms that did not require respiratory support or intervention, and had no clearly documented alternative explanation. Moderate disease was defined as symptoms consistent with COVID-19 that required respiratory support, but did not require invasive positive pressure ventilation (IPPV) or extracorporeal membrane oxygenation (ECMO). Severe disease was defined as symptoms consistent with COVID-19 that required IPPV or ECMO. Patients who were on a ventilator at admission, such as those on home oxygen therapy or who were originally fitted with a ventilator in a facility, were excluded from the severe disease category. Patients with symptoms unrelated to COVID-19, and who were on a ventilator for airway maintenance, were also excluded.

In COVID-19 wards, close monitoring and rapid response were difficult due to infection prevention issues. For this reason, the threshold for admission to the PICU was set lower than the admission criteria for patients without COVID-19. Therefore, asymptomatic patients after scheduled or emergency surgery, or patients who were not in respiratory failure, but who required close monitoring because of epileptic seizure, metabolic or endocrine diseases, or myocarditis, were also indicated for admission to the PICU.

Close contacts were defined as individuals who were in contact with the patients for at least 15 minutes without taking the necessary infection prevention measures and at a distance such that they could touch them with their hands, 2 days before the date of onset [4]. Patients were identified as having multisystem inflammatory syndrome in children (MIS-C) if that was the discharge diagnosis by the physician who provided the clinical care, and if they met the Centers for Disease Control and Prevention criteria for MIS-C [9].

Treatment/vaccination

The national guidelines on treatment regimens for COVID-19 in pediatric patients initially permitted the use of various antiviral drugs at the discretion of physicians at each medical facility. Subsequently, in May 2020, remdesivir was approved to shorten the duration of symptoms in patients with pneumonia, and the indication was expanded to reduce the risk of severe disease. In July 2020, dexamethasone was also included in the guidelines as an anti-inflammatory drug for patients with pneumonia associated with hypoxemia [5].

In Japan, mRNA vaccines have been mostly used. Compared with those in Western countries, such as the UK and the US, the introduction of COVID-19 vaccines in Japan was initially delayed, due to domestic regulations. Because of this delay in vaccine introduction, priority was given to those who were most eligible for vaccination. Healthcare workers were given priority as the first group to be vaccinated, as from February 17, 2021, followed by those in the general population ≥ 65 years old, from April 12, 2021. The targeted age groups were then expanded sequentially. A third dose of mRNA COVID-19 vaccine became available on December 1, 2021, to boost immunity. Japan achieved high vaccination coverage — as of January 2022, ≥ 75% of the population had received a second dose of COVID-19 vaccine, and approximately 90% of those aged ≥ 65 years were fully vaccinated. In children, eligibility for COVID-19 vaccine was expanded to those aged ≥ 12 from June 2021, and the first vaccine dose for those aged 5–11 was approved in January 2022.

Data sources/measurements

The electronic medical records of all patients hospitalized at our centers during the study period were manually reviewed to obtain the following: demographic, clinical, and laboratory data; reasons for admis-

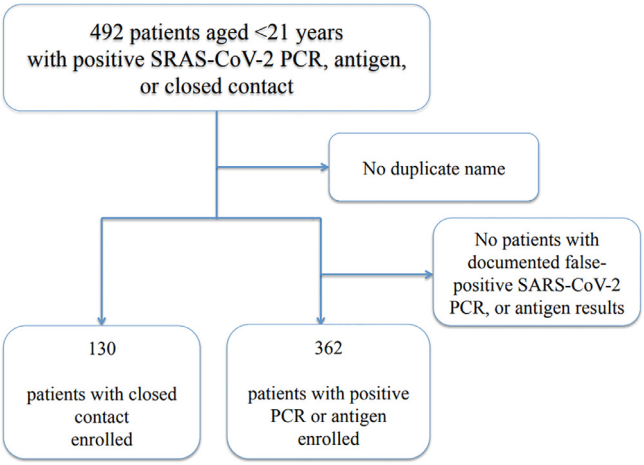

Figure 1. Flow diagram for selection of patients included in the study.

sion; specific treatments; and hospitalization outcome data, from admission to discharge. The compiled data were maintained electronically onsite, in accordance with the institutional review board protocol. Chart reviews were conducted by two authors.

Statistical methods

Categorical and continuous variables were expressed as number (%) and median (interquartile range [IQR]), respectively. Comparisons between the two groups were performed using Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. The Kruskal–Wallis test and Bonferroni correction were used to analyze continuous variables for each severity. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBMS Corp., Armonk, NY, USA).

Results

During the study period, 492 patients with COVID-19 and close contacts were admitted, including 106, 90, 228, and 68 admitted at Aichi Children's Health and Medical Center, Hyogo Prefectural Kobe Children's Hospital, Osaka Women's and Children's Hospital, and Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, respectively. No duplicate names were identified. In total, 130 (26.4%) patients had negative SARS-CoV-2 PCR results but were close contacts (Figure 1). During the chart review, none of the patients had false-positive SARS-CoV-2 PCR results.

The patients' background characteristics are shown in Table 1. The median age was 3.0 years (interquartile range [IQR] 0–9 years) and 289 (58.7%) were male. Among the 232 (47.2%) patients with underlying diseases, the most common condition was neurological or neuromuscular disease ($n = 97$, 19.7%), followed by chronic heart disease ($n = 48$, 9.8%), and chronic respiratory disease ($n = 43$, 8.7%). Only 14 of the patients aged ≥ 5 years ($n = 14/201$, 7.0%) had received two doses of the SARS-CoV-2 vaccine. No history of vaccination was reported in 137 patients.

Table 2 presents data comparing severity and outcomes. Most patients were asymptomatic or had mild disease ($n = 451$, 91.7%), while severe disease accounted for the lowest number of patients (n = 11, 2.2%). Specific treatments for COVID-19, including remdesivir and dexamethasone, were administered for 9.6% ($n = 47$) of patients. Invasive mechanical ventilation was required in 6.9% of the patients ($n = 34$), whereas none required ECMO support. There was no MIS-C case. The median length of hospital stay (LOS) was 4.0 (IQR 3.0–8.0) days. Two deaths (0.4%) occurred in this study population. These deaths were caused by suffocation and encephalopathy. The encephalopathy case may have been attributed to COVID-19.

Table 1
Background characteristics of the study cohort.

Variable	Subcategory	Total
Number of cases		492
Age	Years, median	3 (0–9)
	< 1 year, number (%)	145 (29.5)
	1–5 years, number (%)	145 (29.5)
	≥ 5 years	201 (40.9)
Sex	Male number (%)	289 (58.7)
Underlying disease	Any, number (%)	232 (47.2)
	Neurological and neuromuscular disease	97 (19.7)
	Chronic heart disease	48 (9.8)
	Hematological disease and malignancy	21 (4.3)
	Metabolic and endocrine disease	16 (3.3)
	Immunosuppressive state	14 (2.8)
	Gastrointestinal disease	11 (2.2)
	Chronic renal disease	8 (1.6)
	Collagen and allergic disease	6 (1.2)
	Others	21 (4.3)
Positive test	Number (%)	362 (73.6)
Close contact	Number (%) with COVID-19 cases	130 (26.4)
SARS-CoV-2-vaccinated patients	One dose, number (%)	3/201 (1.5)
	Two doses number (%)	14/201 (7.0)

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2
Comparison of severity and outcomes.

Variable	Subcategory	Total
Number of cases		492
Severity	Close contact, number (%)	130 (26.4)
	Asymptomatic, number (%)	48 (9.8)
	Mild, number (%)	273 (55.5)
	Moderate, number (%)	30 (6.1)
	Severe, number (%)	11 (4.5)
Specific treatment (%) for COVID-19, number		47 (9.6)
Invasive mechanical ventilation/ECMO, number (%)		34 (6.9)
PICU admission, number (%)		51 (10.4)
Death, number (%)		2 (0.4)
Length of hospital stay (days), median (IQR)		4.0 (3–8)

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; PICU, pediatric intensive care unit; IQR, interquartile range.

Table 3 presents the characteristics and statistical analyses for each disease severity group. The median ages and sexes of the patients were similar across the groups. Patients with underlying diseases differed significantly in terms of disease severity ($p = 0.026$). Underlying diseases were more common in close contacts or patients with asymptomatic disease than in those with mild disease. With the exception of close contacts and patients with asymptomatic disease, lower respiratory symptoms ($p < 0.001$) were less common in patients with mild disease than in those with moderate or severe disease), while neurological symptoms ($p = 0.007$) were more common in patients with mild or severe disease than in those with moderate disease.

The reasons for hospitalization differed — treatment of COVID-19 symptoms was less common in patients with asymptomatic and mild diseases ($p < 0.001$). In contrast, social reasons were more common in patients with mild disease, mainly due to facility factors, such as difficulty with isolation in public assistance facilities and refusal of hospitalization by other hospitals due to COVID-19 diagnosis, resulting from a lack of available beds for pediatric COVID-19, insufficient personnel to deal with COVID-19, or a hospital policy not to accept pediatric patients with COVID-19 ($p < 0.001$). The median LOS differed substantially among these groups, with significantly longer LOS in patients with severe disease ($p < 0.001$). There was a significantly higher rate of invasive mechanical ventilation and PICU admission in patients with severe disease ($p < 0.001$).

Table 3
Characteristics and statistical analysis according to disease severity.

Variable	Close contacts	Asymptomatic	Mild	Moderate	Severe	*p*-value
Number of cases	130	48	273	30	11	
Age, years, median (IQR)	2 (0–8)	1 (0–8)	4 (1–9)	2 (0.25–12)	2 (0–8.5)	0.053
Male sex, number (%)	68 (52.3)	34 (70.8)	168 (61.5)	15 (50.0)	4 (36.4)	0.063
Any underlying disease, number (%)	71 (54.6)	28 (58.3)	111 (40.7)	17 (56.7)	5 (45.5)	0.026
Symptoms[a]						
History of fever, number (%)	0	0	237 (86.8)	28 (93.3)	9 (81.8)	0.513
History of upper respiratory symptoms, number (%)	0	0	71 (26.0)	5 (16.7)	1 (9.1)	0.255
History of lower respiratory symptoms, number (%)	0	0	11 (4.0)	11 (36.7)	3 (27.3)	< 0.001
History of GI, number (%)	0	0	31 (11.4)	2 (6.7)	0	0.375
History of neurological symptoms, number (%)	0	0	54 (19.8)	1 (3.3)	5 (45.5)	0.007
Reason for hospitalization						
Treatment of COVID-19 patients on admission, number (%)	6 (4.6)	1 (2.1)	41 (15.0)	19 (63.3)	9 (81.8)	< 0.001
Social reason for admission, number (%)	25 (19.2)	22 (45.8)	131 (48.0)	4 (13.3)	0	< 0.001
Lack of family support	12	5	31	0	0	0.388
Difficulty due to isolation or during hospitalization	13	17	100	4	0	< 0.001
LOS, days, median (IQR)	5.0 (3–8)	3.0 (3–7)	4.0 (3–7)	6.0 (5–9.75)	13.0 (9.5–16)	< 0.001
IPPV, number (%)	9 (6.9)	3 (6.3)	10 (3.7)	1 (3.3)	11 (100.0)	< 0.001
PICU admission, number (%)	7 (5.4)	5 (10.4)	15 (5.5)	13 (43.3)	11 (100.0)	< 0.001
Death, number (%)	0	0	0	0	2 (18.2)	

GI, gastrointestinal symptoms; COVID-19, coronavirus disease 2019; LOS, length of hospital stay; IPPV, invasive positive pressure ventilation; PICU, pediatric intensive care unit; IQR, interquartile range.

[a] Analyses by history of symptoms were in accordance with disease category (mild, moderate, and severe).

Discussion

This study revealed that cases of asymptomatic and mildly symptomatic disease accounted for a large proportion of the hospital burden. Some patients were hospitalized for social reasons. Lower respiratory and neurological symptoms were more common, and the degree of medical intervention was higher, in patients with severe disease.

Hospitalization rates for pediatric COVID-19 are increasing in many countries, including Japan [2,3]. Data on the severity of disease caused by the Omicron variant are limited, but they show less severity than the Delta and other variants [10–13]. Some nationwide studies have compared the characteristics of pediatric COVID-19 before and during the Omicron-predominant period in Japan. Shoji et al. showed that more pediatric patients experienced fever and seizure in the Omicron-predominant period; however, the overall severity was similar, and no patients died in either period [14]. Hiroyuki et al. reported that more pediatric patients experienced croup syndrome in the Omicron-predominant period; however, most patients had non-severe disease in either period [15].

Several hypotheses have been proposed to explain this explosive rise in the number of children affected. First, the Omicron variant is more contagious than Delta and other variants [16]. Second, children aged < 5 years were not eligible for COVID-19 vaccination, and children aged 5–11 years were not eligible for boosters. However, for COVID-19, the medical care system had mainly been established with a focus on adults. Consequently, the pediatric healthcare system was lagging behind, especially in Japan's inpatient system. Moreover, pediatric COVID-19 patients generally require more medical and nursing care than patients with other viral infections or adult COVID-19 patients. Pediatric patients require more daily care and have difficulty controlling their behavior, leading to an increased risk of transmission to medical staff. Therefore, pediatric patients with COVID-19 are admitted to a limited number of medical facilities, further increasing the burden on these facilities [17]. Hospitalization of parents or guardians is one solution; however, this is difficult in children's hospitals because of the impossibility of treating and caring for adult patients. Administrative support for hospitals is inadequate, and an insufficient number of facilities capable of accepting inpatients and a lack of accommodation for patients with social problems are major concerns.

In our study, most of the patients were asymptomatic and had mild disease. Some of these patients were admitted for social reasons, such as lack of family support, difficulty with isolation in public assistance facilities, and refusal of hospitalization by other centers. Although the median length of stay was short, the total number of patients was large, making it a significant burden of disease. There have been few studies of the social reasons for hospitalization in pediatric COVID-19 patients. Our hospitals are specialized medical facilities for severe and complicated pediatric patients; however, this study showed that a large proportion of hospitalized children were categorized as asymptomatic or mild disease and were admitted for social reasons. This resulted in a high disease burden in our hospitals, with beds occupied by severely ill patients for several days, restriction of new admissions for other diseases for a number of months, and postponement of scheduled surgeries. To maintain a system of medical care for critically ill patients, these patients should either be admitted to the accommodation facilities or treated at home.

This study did not show any association between hospitalization and vaccination severity, because the number of vaccinated children during the study period was small, and information about vaccination status was missing for some patients.

Our study had several limitations. First, the data were obtained from four tertiary medical centers specifically for children. Therefore, the relevance of our findings to other medical facilities remains unclear. Second, our data had no information on the specific variant strain detected in each patient; therefore, it was not possible to assess the direct effect of variant strain on the clinical characteristics. However, data from the National Institute of Infectious Diseases revealed that more than 95% of the variant strains detected in Japan during the Omicron-predominant period were Omicron type [4]. This suggests that the impact of missing variant strain data may be minimal. Third, our definition of disease severity may be inappropriate for pediatric COVID-19 patients. Early infant fever, febrile convulsion, and croup syndrome are not considered indicators of severe infection; however, in general, they require hospitalization. Previous reports have described that non-respiratory symptoms, including MIS-C and encephalopathy, account for a high percentage of patients admitted to the PICU [18]. In our study, infant fever and neurological symptoms, including febrile convulsion, were the major symptoms at admission, but many of these patients were categorized as showing mild symptomatic infections. Only 15 (30.0%) patients admitted to the PICU developed severe infection during the study period. Therefore, an alternative definition of severity in children is required.

In conclusion, the disease burden was attributed to cases of asymptomatic and mild disease during the Omicron variant-predominant period. Some of the patients were hospitalized for social reasons. To maintain a medical care system for critically ill patients, each medical facil-

ity must play a role according to its function. Administrative support is needed to increase the number of hospitals providing medical care for pediatric COVID-19 patients and to accommodate patients and their families with social problems.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Not applicable

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Ethical approval statement

This study was approved by the institutional review board (no. R4-63). Informed consent was obtained from parents using the opt-out method.

Contributors

SM conceptualized the study, collected, analyzed, and interpreted the data, drafted the initial manuscript, and critically reviewed and revised the manuscript. EO, MN, YC, and MK collected the data, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

Data sharing

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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