



Clinical Characteristics of Hospitalized COVID-19 in Children: Report From the COVID-19 Registry in Japan

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A total of 1038 pediatric patients with COVID-19 were identified. Among these, 308 (30%) had asymptomatic COVID-19. The overall outcome was good, and no patients died. A significant rate of patients aged <24 months and ≥13 years were found in the symptomatic group.

Key words. children; coronavirus disease 2019; epidemiology; severe acute respiratory syndrome coronavirus 2.

Coronavirus disease 2019 (COVID-19), an emerging respiratory infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread worldwide.

Compared with adults, SARS-CoV-2 infection follows a relatively mild clinical course in children. However, several studies suggest that SARS-CoV-2 infection might be severe in children with underlying medical conditions including chronic lung or heart disease, malignancy, and immunosuppressive conditions [1, 2]. Furthermore, in children without any underlying conditions, SARS-CoV-2 infection might be fatal due to multisystem inflammatory syndrome (MIS-C) [3]. Therefore, SARS-CoV-2 infection remains a serious concern in children. Despite the relatively large proportion of asymptomatic pediatric patients with SARS-CoV-2 infection, information regarding the differences between asymptomatic and symptomatic pediatric patients remain very limited [4].

COVID-19 registry in Japan (COVIREGI-JP) is the largest registry of hospitalized patients with SARS-CoV-2 infection in

Japan [5]. The present study aimed to describe the clinical and epidemiological characteristics of pediatric SARS-CoV-2 infection in Japan, with a specific focus on differences between symptomatic and asymptomatic pediatric patients using the data from COVIREGI-JP.

PATIENTS AND METHODS

COVIREGI-JP

The details of COVIREGI-JP have been previously described [5]. Briefly, hospitalized patients who were positive for SARS-CoV-2 based on nucleic acid amplification (NAT) test or rapid antigen test were enrolled in the registry.

Study Design and Patient Populations

This was a retrospective observational study using the data from COVIREGI-JP. Pediatric patients under 18 years of age who were enrolled in COVIREGI-JP between January 1, 2020 and February 28, 2021, were included in the present study. The demographic and epidemiological data, such as age, sex, underlying diseases, history of COVID-19 exposure, vital signs, signs and symptoms, treatment, duration of hospitalization, and outcomes, were extracted from the database.

Statistical Analysis

Clinical and epidemiological data were compared between symptomatic and asymptomatic patients as well as among patients in specific age categories. Fisher's exact test was used for the comparison of categorical variables, and the Mann-Whitney *U* test was used for 2 group comparisons of continuous variables, respectively. A 2-sided *P* value of <.05 was considered to indicate statistical significance. All statistical analyses were performed by the R statistical software version 4.0.5.

Ethics Approval

The National Center for Global Health and Medicine ethics review committee and the National Center for Child Health and Development ethics committee approved the study (NCGM-G-003494-0 and NCCHD-2020-313, respectively).

RESULTS

During the study period, a total of 36 430 patients with SARS-CoV-2 infection who were hospitalized in 572 institutions were registered in COVIREGI-JP. Among these, 1038 pediatric patients were hospitalized with SARS-CoV-2 infection. The background characteristics of these pediatric patients are summarized in Table 1. Briefly, the median cohort age was 9.0 years, 169 (16.3%) patients were younger than 24 months of age, and 571 (55.0%) patients were male. The rate of patients with

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underlying conditions was very low (n = 60 [5.8%]). Although the cohort included only hospitalized cases, 308 (29.7%) of the patients were asymptomatic at the time of admission.

Comparison of the Background Characteristics Between Symptomatic and Asymptomatic Patients

The comparison of asymptomatic and symptomatic patients is shown in Table 1. The distribution of age was significantly different between the asymptomatic and symptomatic groups ($P < .001$). Specifically, the rates of patients aged <24 months and ≥ 13 years were higher in the symptomatic group than in the asymptomatic group. Although not statistically significant, the rate of patients with any underlying disease was higher in the symptomatic group than in the asymptomatic group (n = 49 [6.7%] vs n = 11 [3.6%], $P = .057$). Other characteristics including sex and immunosuppressive conditions were similar between the 2 groups.

The comparisons of laboratory data between the symptomatic and asymptomatic patients categorized according to age (Supplementary Figure S1) revealed that the majority of laboratory data were comparable between the asymptomatic and symptomatic groups.

We performed supplementary analyses to compare disease severity according to the different “wave periods.” We divided the patients into 2 groups: patients hospitalized from January 2020 to September 2020 and those hospitalized from October 2020 to February 2021. The number of patients who required supplemental oxygenation was similar in the 2 groups, 5/312 (1.6%) and 10/418 (2.4%), respectively ($P = .601$).

Clinical Characteristics of the Symptomatic Patients

The clinical characteristics of the symptomatic patients are shown in Table 2. In this group, the most commonly observed symptoms were cough (n = 271 [37.1%]) and runny nose

Table 1. Background Characteristics of the Study Cohort

Variables	Number of Cases	Subcategories	Total	Asymptomatic on Admission	Symptomatic on Admission	P Value ^e
Case number	1038		1038	308 ^d	730	NA
Age (years), median (IQR)	1038		9.0 (3.0-14.0)	8.0 (4.0-12.0)	10.5 (3.0-15.0)	<.001
Age category, number (%)	1038	0 to <3 months	17 (1.6)	3 (1.0)	14 (1.9)	<.001
		3 to <24 months	152 (14.6)	31 (10.1)	121 (16.6)	
		2 to <6 years	190 (18.3)	78 (25.3)	112 (15.3)	
		6 to <13 years	313 (30.2)	130 (42.2)	183 (25.1)	
		≥ 13 years	366 (35.3)	66 (21.4)	300 (41.1)	
Sex, number (%)	1038	Male	571 (55.0)	171 (55.5)	400 (54.8)	.838
		Female	467 (45.0)	137 (44.5)	330 (45.2)	
Underlying disease ^a , number (%)	1038	Any underlying diseases	60 (5.8)	11 (3.6)	49 (6.7)	.057
		Bronchial asthma	36 (3.5)	6 (1.9)	30 (4.1)	.095
		Obesity	8 (0.8)	1 (0.3)	7 (1.0)	.448
		Congenital heart anomaly	5 (0.5)	1 (0.3)	4 (0.5)	1.0
		Diabetes without complication	4 (0.4)	1 (0.3)	3 (0.4)	1.0
		Congenital anomaly or chromosomal abnormality	3 (0.3)	0 (0.0)	3 (0.4)	.559
		Hypertension	2 (0.2)	1 (0.3)	1 (0.1)	.506
		Others ^b	7 (0.7)	2 (0.6)	5 (0.7)	1.0
Immunosuppressive condition, number (%)	1038		6 (0.6)	2 (0.6)	4 (0.5)	1.0
Exposure within 14 days prior to admission	1034	Travel abroad	35 (3.4)	15 (4.9)	20 (2.8)	.034
	1035	Close contact with COVID-19 cases	854 (82.5)	284 (92.2)	570 (78.4)	<.001
	854	Family	673 (78.8)	228 (80.3)	445 (78.1)	.478
	854	Educational facility	126 (14.8)	37 (13.0)	89 (15.6)	.357
	854	Health care facility	2 (0.2)	2 (0.7)	0 (0.0)	.110
	854	Nonfamily roommates	12 (1.4)	1 (0.4)	11 (1.9)	.071
	854	Workplace	2 (0.2)	0 (0.0)	2 (0.4)	1.0
	854	Others	41 (4.8)	19 (6.7)	22 (3.9)	.088
Days of hospitalization from symptom onset, median (IQR)	709		3.0 (1.0-5.0)	–	3.0 (1.0-5.0)	NA

Abbreviations: IQR, interquartile range; NA, not applicable.

^aNo patients had the following underlying diseases: myocardial infarction, dementia, chronic obstructive pulmonary disease, chronic lung disease, mild liver disease, moderate to severe liver dysfunction, peptic ulcer, diabetes with complications, lymphoma, metastatic solid tumor, and human immunodeficiency virus infection.

^bOther diseases, including the following underlying conditions: congestive heart failure, cerebrovascular disease, peripheral vascular disease, paralysis, hyperlipidemia, solid tumor, leukemia, and collagen disease.

^cFisher's exact and the Kruskal-Wallis rank-sum tests were used for comparisons of categorical and continuous variables, respectively.

^dAmong 308 asymptomatic patients on admission, 46 (14.9%) develop one or more of the following symptoms during hospitalization: fever $\geq 38.0^{\circ}\text{C}$ (n = 4), saturated oxygen in arterial blood <96% (n = 10), tachycardia (n = 22), and tachypnea (n = 14).

Table 2. Clinical Characteristics on Admission of Symptomatic Patients

Patient Characteristics	Number of Cases	Subcategories	Total (n = 730)	<3 Months	3 To <24 Months	2 to <6 Years	6 to <13 Years	≥13 Years
Number of cases	730		730	14	121	112	183	300
Fever ≥38.0°C	730		75 (10.3)	2 (14.3)	29 (24.0)	17 (15.2)	7 (3.8)	20 (6.7)
SpO ₂ < 96% under room air	699		41 (5.9)	3 (21.4)	15 (13.5)	5 (5.0)	9 (5.1)	9 (3.0)
Cough	730		271 (37.1)	2 (14.3)	38 (31.4)	42 (37.5)	65 (35.5)	124 (41.3)
Fatigue	730		92 (12.6)	1 (7.1)	2 (1.7)	2 (1.8)	18 (9.8)	69 (23.0)
Shortness of breath	730		16 (2.2)	0 (0.0)	1 (0.8)	2 (1.8)	3 (1.6)	10 (3.3)
Diarrhea	728		65 (8.9)	0 (0.0)	8 (6.6)	5 (4.5)	16 (8.7)	36 (12.0)
Sore throat	729		120 (16.5)	0 (0.0)	1 (0.8)	9 (8.0)	24 (13.1)	86 (28.7)
Headache	729		103 (14.1)	0 (0.0)	0 (0.0)	1 (0.9)	25 (13.7)	77 (25.8)
Dysgeusia	730		95 (13.0)	0 (0.0)	0 (0.0)	3 (2.7)	18 (9.8)	74 (24.7)
Olfactory dysfunction	729		82 (11.2)	0 (0.0)	0 (0.0)	0 (0.0)	11 (6.0)	71 (23.7)
Runny nose	730		215 (29.5)	1 (7.1)	55 (45.5)	38 (33.9)	52 (28.4)	69 (23.0)
Arthralgia/myalgia	729		20 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)	16 (5.3)
Vomiting	730		22 (3.0)	0 (0.0)	3 (2.5)	2 (1.8)	9 (4.9)	8 (2.7)
Wheezing	730		10 (1.4)	0 (0.0)	6 (5.0)	3 (2.7)	1 (0.5)	0 (0.0)
Chest pain	729		4 (0.5)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	3 (1.0)
Abdominal pain	730		21 (2.9)	0 (0.0)	1 (0.8)	3 (2.7)	4 (2.2)	13 (4.3)
Conjunctivitis	727		5 (0.7)	0 (0.0)	0 (0.0)	2 (1.8)	2 (1.1)	1 (0.3)
Rash	727		6 (0.8)	0 (0.0)	3 (2.5)	1 (0.9)	0 (0.0)	2 (0.7)
Chest X-ray	393	No abnormalities	358(91.1)	6 (75.0)	42 (84.0)	31 (79.5)	90 (98.9)	189 (92.2)
		Pneumonia	34 (8.7)	2 (25.0)	8 (16.0)	8 (20.5)	0 (0.0)	16 (7.8)
		Other abnormalities	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Chest computed tomography	200	No abnormalities	171 (85.5)	1 (100.0)	5 (62.5)	2 (66.7)	22 (84.6)	141 (87.0)
		Pneumonia	27 (13.5)	0 (0.0)	3 (37.5)	1 (33.3)	3 (11.5)	20 (12.3)
		Other abnormalities	2 (1.0)	0(0.0)	0 (0.0)	0 (0.0)	1 (3.8)	1 (0.6)

Abbreviation: SpO₂, saturated oxygen in arterial blood.

(n = 215 [29.5%]). Fever ≥38.0°C was observed in only 75 (10%) of the symptomatic patients. Several symptoms, such as diarrhea, dysgeusia, and olfactory dysfunction, were more commonly observed in older patients than in younger patients.

Interventions and Outcomes

The clinical interventions and outcomes of the symptomatic pediatric SARS-CoV-2 infection patients are summarized in [Supplementary Table S1](#) and [Supplementary Digital Content](#). Only 15 (2.1%) patients required noninvasive oxygen support, and no patient needed invasive mechanical ventilation or extracorporeal membrane oxygenation. The outcomes were good and there was no mortality.

Although the majority of the patients had asymptomatic or mild SARS-CoV-2 infection, the median duration of hospitalization was 8 (interquartile range, 6-9) days; the duration of hospitalization was not different between the symptomatic and asymptomatic patients (8 [5-9]) and 8 [6-9] days, respectively).

DISCUSSION

In this nationwide observational study of hospitalized pediatric patients with SARS-CoV-2 infection conducted in Japan, our analyses revealed that neonates and young infants tended to be symptomatic.

Our analyses revealed that the rate of symptomatic patients was relatively high in neonates and young infants compared to the other age groups. Whether young children, such as neonates or infants, are at risk of developing symptoms has not been extensively investigated. A national prospective surveillance study in France revealed that fever was more common in pediatric patients aged <90 days than in those from other age groups [6]. Additionally, a study reported that dyspnea, sore throat, and cough were more common in newborn patients than in infants, which might be related to an immature immune system [7]. Consistent with these reports, our results indicate that symptoms might be more common in very young patients.

In the current study, the outcome of hospitalization was excellent, with no patient deaths. International, multicenter cohort studies in Europe and Latin America show that intensive care unit admission rate range between 8.2% and 12.7% in pediatric patients with SARS-CoV-2 infection and that the mortality rate ranges between 0.7% and 4.2% in hospitalized pediatric patients [1, 2]. The cause underlying the excellent outcome observed in the current cohort is not clear but one potential explanation is the rarity of MIS-C in Japan. MIS-C, which is a severe inflammatory condition that emerges several weeks after SARS-CoV-2 infection, can be severe and even fatal; however, MIS-C appears to be more common in Black, Caucasian, and Latin American ethnic groups and has been rarely reported

in Asians [8]. In fact, only two cases of MIS-C have been reported in Japan [9, 10]. Moreover, the low proportion of patients with an underlying condition in our cohort could be a potential explanation of the excellent outcome. Those patients with underlying diseases and/or their family members might have faithfully adhered to infection control measures, including social distancing, hand hygiene, universal masking, or home isolation, which may have also contributed to the very low proportion of patients with underlying conditions.

Although the majority of pediatric patients in Japan had asymptomatic or mild SARS-CoV-2 infection, the median hospitalization duration was longer than 1 week. The COVIREGI-JP did not include information regarding the primary reason for admission. However, mild or asymptomatic SARS-CoV-2 positive patients were admitted to the hospital for isolation purposes, especially in the early stage of the COVID-19 pandemic. In addition, we received many pediatric hospitalized cases for isolation because both parents of some children were hospitalized with severe COVID-19, and no other family members could take care of the children. Thus, we believe that the primary reason for hospitalization among asymptomatic pediatric patients was isolation. There are many disadvantages associated with hospitalization in children. Therefore, it may be necessary to reconsider the current indications for hospitalization and in-hospital isolation duration for pediatric patients with SARS-CoV-2 infection in Japan.

The present study has several limitations. First, participation in this registry was voluntary; therefore, the data might not have reflected the overall epidemiology of pediatric SARS-CoV-2 infection in Japan. Second, COVIREGI-JP included only hospitalized patients and not outpatients. Therefore, the findings of the present study cannot be generalized to outpatient settings. Third, the prevalence of symptoms across age groups should be carefully interpreted. Younger children are not going to be able to accurately describe symptoms such as dysgeusia or olfactory dysfunction. Thus, the prevalence of these symptoms in younger children would have been underestimated. Fourth, COVIREGI-JP did not have information on long-term outcomes of acute infection, such as MIS-C and the increasingly reported long COVID [11].

In conclusion, our analyses of the clinical and epidemiological data of COVIREGI-JP revealed that the majority of pediatric patients had mild or asymptomatic SARS-CoV-2 infection and that neonates and young infants tended to be symptomatic.

Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online.

Notes

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Potential conflicts of interest. All authors declare that they do not have any potential, perceived, or real conflicts of interest. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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