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Original Article

Clinical characteristics and factors associated with severe COVID-19 in hospitalized children during the SARS-CoV-2 Omicron pandemic in Taiwan

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Abstract *Background:* Since April 2022, a notable increase in COVID-19 cases with the rapid spread of the SARS-CoV-2 Omicron variant has been reported in Taiwan. In the epidemic, children were one of the most vulnerable groups, so we analyzed their clinical presentations and factors associated with severe complications of COVID-19 in children.
Methods: We included hospitalized patients under 18 years old with lab-confirmed SARS-CoV-2 infection from March 1, 2022, to July 31, 2022. We collected the demographic and clinical characteristics of the patients. Patients requiring intensive care were defined as severe cases.
Results: Among the 339 enrolled patients, the median age was 31 months (interquartile range (IQR), 8—79.0 months); and 96 patients (28.3%) had underlying diseases. Fever was noted in 319 patients (94.1%) with a median duration of two days (IQR 2—3 days). Twenty-two patients (6.5%) were severe cases, including 10 patients (2.9%) with encephalopathy with abnormal neuroimaging and ten patients (2.9%) with shock. Two patients (0.6%) died. Patients with congenital cardiovascular disease (aOR: 21.689), duration of fever up to four days or more (aOR: 6.466), desaturation (aOR: 16.081), seizure (aOR: 20.92), and procalcitonin >0.5 ng/mL (aOR: 7.886) had a higher risk of severe COVID-19.

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Conclusions: Vital signs need close monitoring, early management and/or intensive care may be applied in COVID-19 patients with congenital cardiovascular diseases, fever lasting ≥4 days, seizures, desaturation and/or elevated procalcition since they are at higher risks of severe diseases.

Introduction

As of September 2022, more than 600 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were documented worldwide. More than 6.4 million deaths have been caused by coronavirus disease 2019 (COVID-19).[1] In December 2021, the Omicron variant (B.1.1.529) of SARS-CoV-2 rapidly spread in the United States (U.S.) according to the national SARS-CoV-2 genomic surveillance program from the Centers for Disease Control and Prevention (CDC).[2]

In Taiwan, the first nonimported case infected by the Omicron variant was pronounced in January 2022. Since March 2022, an epidemic of COVID-19 dominated by the Omicron variant (B.A.1. and B.A.2.) has been reported in Taiwan.[3] According to data from Taiwan CDC, there were only 14,603 people infected by SARS-CoV-2 from 2020 to 2021. However, more than 5.5 million people were infected by the virus between January 2022 and September 2022 in Taiwan. Among infected people, over 1.1 million people were under 19 years old (20.5%). Children aged between one and nine years presented the highest incidence (more than 30 thousand per 100 thousand people) of SARS-CoV-2 infection among all age groups.[4] Some studies before the Omicron wave reported that children with underlying diseases, such as congenital heart disease, chronic lung disease, neurological diseases and obesity, and elevated levels of CRP or D-dimer in laboratory data might be associated with a higher risk for poor outcomes.[5,6] However, data in the era of the Omicron variant are still lacking in identifying predictors of severe COVID-19.

Our objective was to provide demographic characteristics, clinical manifestations, laboratory data, and clinical outcomes of hospitalized children or adolescents with SARS-CoV-2 infection under the Omicron predominance in Taiwan. We would like to define clinically significant predictors associated with severe COVID-19 in children in the Omicron wave so that early management of high-risk patients could be implemented to improve their clinical outcomes.

Methods

Case inclusion criteria

This retrospective cohort study was conducted at National Taiwan University Hospital (NTUH) from March 1, 2022, to July 31, 2022. We included hospitalized patients under 18 years old with lab-confirmed acute and symptomatic SARS-CoV-2 infection, which was defined by an index positive SARS-CoV-2 polymerase chain reaction (PCR) or antigen (Ag) test result within 14 days before admission or during hospitalization.

Data collection and definition of laboratory results

We collected demographic data, including age, sex, body height, weight, underlying diseases,and vaccination status, from electronic medical records at National Taiwan University Hospital. Underlying diseases included congenital cardiovascular disease, neurological diseases, hematologic diseases and other malignancies, diseases of the gastrointestinal tract and hepatobiliary tract, endocrinologic/metabolic diseases, immunological diseases, asthma and other allergic diseases, chronic lung disease and other airway anomalies, and/or multiple underlying diseases.

Clinical characteristics, including vital signs, laboratory data upon admission, chest X-ray, medications, and outcomes, were extracted from the system as well. For RT-PCR, nasopharyngeal swabs were taken by pediatricians after agreement of the patient or the parent. RT-PCR was performed by a Roche cobas SARS-CoV-2 assay (Roche Molecular Systems, Branchburg, NJ, USA) with three unique TaqMan probes targeting conserved regions within the ORF (open reading frame) 1 ab and E genes.[7] Ct values were provided by the testing platform based on manufacturer-provided interpretation criteria.

An oxygen saturation value ≤ 94% measured by oximeter was defined as desaturation. The oxygen saturation we documented was measured at emergency room or upon admission to the ward. Abnormal creatinine was defined as a patient with creatinine levels higher than the upper limit of age-appropriate values.[8] Neutrophilia was defined as a patient with an absolute neutrophil count higher than the upper limit of age-appropriate values. Leukopenia was defined as a white cell count lower than the lower limit of age-appropriate values.[9] Thrombocytopenia was defined as a platelet count <150,000/microliter. The laboratory data were measured from the blood samples obtained upon admission.

Definition of clinical severity and diagnoses

We categorized the hospitalized patients into "nonsevere" and "severe" groups. The definition of "severe" was modified from the maximum Clinical Progression Scale (CPS) score created by the World Health Organization (WHO) for COVID-19 clinical research.[10] Patients requiring intensive care (including shock needing aggressive fluid supplement, vasopressors or inotropes, respiratory distress requiring invasive or non-invasive ventilator, neurological

symptoms such as new-onset seizure with focal neurological signs, change of consciousness, or status epilepticus), extracorporeal membrane oxygenation (ECMO), or death were separated into the "severe" group. The other conditions were sorted as the "nonsevere" group, including patients admitted to the ICU for invasive procedures without requiring intensive care.

The definition of clinical diagnosis for croup was defined as hoarseness, stridor, and barking cough. Pneumonia or bronchopneumonia was defined as an abnormality on chest X-ray and crackles revealed by auscultation. Encephalopathy was defined as altered mental status (defined as altered level of consciousness, lethargy, or personality change) lasting $\geq$24 h without alternative cause identified plus two or more minor criteria. Minor criteriae included (1) generalized or partial seizures not fully attributable to a preexisting seizure disorder or febrile convulsion, (2) new onset of focal neurologic findings, (3) abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that appears either acute lesion or new lesion from prior studies, and (4) abnormality on electroencephalography that is consistent with encephalitis.

Statistical analysis

The Kolmogorov–Smirnov test was used to test the normality of the sample distribution. If the data were not normally distributed, the Mann–Whitney U test was used to assess the continuous variables. We used the chi-square test to analyze categorical data. We used ROC curves to determine the cutoff value of continuous variables. Binary logistic regression analysis was used to identify the significant risk factors for severe COVID-19. Unadjusted and adjusted risk ratios are presented with 95% confidence intervals (CIs). We regarded P values < 0.05 as statistically significant. All statistical analyses were performed by using Statistical Product and Service Solutions (SPSS) version 23.

Ethics

This study was approved by the Institutional Review Board of National Taiwan University Hospital (202206053RINC). All data were deidentified before being analyzed. Informed consent was waived due to the nature of the retrospective study in which the analysis was conducted with anonymous clinical data.

Results

Demography

A total of 355 children or adolescents with laboratory-confirmed SARS-CoV-2 infection were found. Fourteen were excluded due to identified evidence of SARS-CoV-2 infection more than 14 days before admission or false-positive results of SARS-CoV-2 PCR. Other two children were excluded due to asymptomatic infection found by screening incidentally. Finally, 339 cases were enrolled in our study. We separated them into "nonsevere" and "severe" groups. There were 22 cases (6.5%) in the severe group. The median interval between disease onset and clinically severe illness was 2 days (IQR: 0–4 days). Six patients developed severe disease after admission with a median interval of 2 days (IQR: 2–3 days).

The demographic data and characteristics of the two groups are shown in Table 1. The median age in patients with severe COVID-19 was older than that in patients in the nonsevere group. Patients older than 72 months were significantly more common in the severe group. Fig. 1 illustrates the overall age distribution of the enrolled children. A significantly higher proportion of patients in the severe group had underlying diseases, including congenital heart diseases, neurological diseases, and multiple underlying diseases.

Clinical manifestations

Clinical manifestations between the two groups are shown in Table 2. Most of the children had a fever (94.1%) with a median duration of two days (IQR: 2.0–3.0 days). Children with severe COVID-19 presented with a longer duration of fever and a higher proportion of fever duration $\geq$4 days (54.5% vs. 16.2%, $p < 0.05$) during the whole disease course, and seizure (36.4% vs. 7.9%, $p < 0.05$) or desaturation (31.8% vs. 3.8%, $p < 0.05$) upon admission. More patients in the nonsevere group complained of rhinorrhea (48.5% vs. 18.2%, $p < 0.05$) or cough (70.7% vs. 36.4%, $p < 0.05$) than the severe cases.

The Supplementary Table S1 showed the most prominent diagnoses of the enrolled patients infected with SARS-CoV-2. Most of the patients had respiratory tract infections, including upper respiratory tract infections (N = 142, 41.9%), croup (N = 32, 9.4%) and pneumonia or bronchopneumonia (N = 23, 6.8%). Encephalopathy was noted in 35 patients (10.3%) who presented with frequent myoclonic jerks, bizarre behavior, hallucinations, or personality changes. Evidence in MRIs and EEGs was found among 10 of them (2.9%). Other severe diseases, such as shock with/without multiorgan failure or acute respiratory distress were noted in 10 patients (2.9%).

Supplementary Table S2 shows the prominent diagnosis of hospitalized patients with desaturation upon admission. All patients with desaturation in the severe group had underlying disease(s). Desaturation was noted in patients with croup, pneumonia, and shock. Supplementary Table S3 demonstrates the underlying disease(s) and associated diagnosis of patients who presented with seizures upon admission. Most of the patients who presented with seizures in the nonsevere group had febrile convulsions or epilepsy. However, most patients who presented with seizures in the severe group had encephalopathy (75.0%).

Laboratory data

Compared with patients in the nonsevere group, more patients with severe COVID-19 had neutrophilia (57.1% vs. 30.9%, $p < 0.05$), procalcitonin $>$0.5 ng/mL (52.9% vs. 11.9%, $p < 0.05$), and abnormally elevated levels of creatinine (18.2% vs. 3.8%, $p < 0.05$) upon admission. No difference in other results of laboratory data was found (Table 3). Among the patients with elevated procalcitonin

Table 1 Demographic characteristics of hospitalized children with SARS-CoV-2 infection.

	All cases (N = 339)	Nonsevere (N = 317)	Severe (N = 22)	P value
Age (month) (Median, IQR)	31.0 (8.0—79.0)	30.0 (7.0—72.5)	81.5 (19.2—117.5)	0.010
Age >72 months	91 (26.7%)	79 (24.9%)	12 (54.5%)	0.002
Gender				
Male/Female[a]	194/145 (1.33)	181/136 (1.33)	13/9 (1.44)	0.855
Underlying diseases[b]				
With underlying disease	96 (28.3%)	84/319 (26.3%)	12/22 (54.5%)	0.005
Congenital cardiovascular disease	15 (4.4%)	11/319 (3.4%)	4/22 (18.2%)	0.011
Neurological diseases	36 (10.6%)	30/319 (9.4%)	6/22 (27.3%)	0.008
Immunological diseases	9 (2.7%)	9/319 (2.8%)	0/22 (0%)	1.000
Hematologic diseases and other malignancy	19 (5.6%)	18/319 (5.7%)	1/22 (4.5%)	1.000
Diseases of GI tract and hepatobiliary tract	6 (1.8%)	6/319 (1.9%)	0/22 (0%)	1.000
Asthma and other allergic disease	9 (2.7%)	9/319 (2.8%)	0/22 (0%)	1.000
Chronic lung disease and other airway anomalies	5 (1.5%)	5/319 (1.6%)	0/22 (0%)	1.000
Endocrinologic/Metabolic diseases	10 (2.9%)	9/319 (2.8%)	1/22 (4.5%)	0.491
Multiple underlying diseases[c]	10 (2.9%)	7/319 (2.2%)	3/22 (13.6%)	0.021
Vaccination status[b]				
Vaccinated	30 (8.8%)	27/319 (8.5%)	3/22 (13.6%)	0.426
Received 1 dose	22 (6.5%)	20/319 (6.3%)	2/22 (9.1%)	0.643
Received 2 doses	8 (2.4%)	7/319 (2.2%)	1/22 (4.5%)	0.417

[a] Data are shown as the case number of male/female (ratio).
[b] Data are shown as case number (%) or case number/case number (%).
[c] Underlying condition involves two or more systems.
N denotes case number; IQR denotes interquartile range.

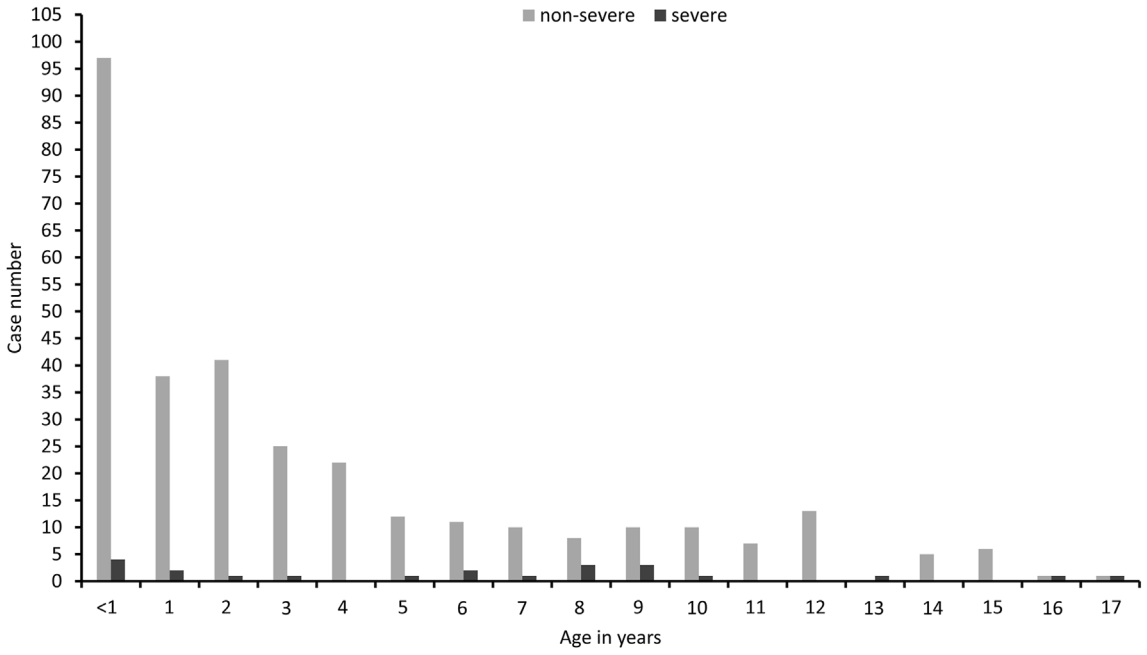

Figure 1. Case numbers of the nonsevere/severe group and age-specific proportion of severe COVID-19 among groups of different ages.

Table 2 Clinical characteristics and outcomes of hospitalized children with COVID-19.

	All cases (N = 339)	Nonsevere (N = 317)	Severe (N = 22)	P value
Contact history				
Household contact	262 (77.3%)	243 (76.7%)	19 (86.4%)	0.431
Community contact	30 (8.8%)	29 (9.1%)	1 (4.5%)	0.707
Nosocomial transmission	7 (2.1%)	7 (2.2%)	0 (0%)	1.000
Unknown	40 (11.8%)	38 (12.0%)	2 (9.1%)	1.000
Symptoms				
Fever	319 (94.1%)	297 (93.7%)	22 (100%)	0.214
Duration (days) (median, IQR)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	4.0 (2.0–4.0)	0.010
Duration of fever ≥4 days	60/319 (18.8%)	48/297 (16.2%)	12/22 (54.5%)	<0.001
Rhinorrhea/nasal congestion	158 (46.6%)	154 (48.5%)	4 (18.2%)	0.006
Cough	232 (68.4%)	224 (70.7%)	8 (36.4%)	0.001
Sore throat	48 (14.2%)	46 (14.5%)	2 (9.1%)	0.487
Hoarseness	27 (8.0%)	26 (8.2%)	1 (4.5%)	0.545
Shortness of breath	58 (17.1%)	52 (16.4%)	6 (27.3%)	0.185
Desaturation	19 (5.6%)	12 (3.8%)	7 (31.8%)	<0.001
Chest pain	6 (1.8%)	6 (1.9%)	0 (0%)	0.516
Abdominal pain	19 (5.6%)	19 (6.0%)	0 (0%)	0.239
Vomiting	80 (23.6%)	77 (24.3%)	3 (13.6%)	0.261
Diarrhea	56 (16.5%)	52 (16.4%)	4 (18.2%)	0.818
Headache	27 (8.0%)	24 (7.6%)	3 (13.6%)	0.304
Seizure	33 (9.7%)	25 (7.9%)	8 (36.4%)	<0.001
Dizziness	10 (2.9%)	9 (2.8%)	1 (4.5%)	0.643
Hallucination	8 (2.4%)	8 (2.5%)	0 (0%)	0.452
Visual illusion	2 (0.6%)	2 (0.6%)	0 (0%)	0.710
Involuntary movement	9 (2.7%)	7 (2.2%)	2 (9.1%)	0.051
Myoclonic jerks	11 (3.2%)	11 (3.5%)	0 (0%)	0.376
Bizarre behavior	9 (2.7%)	7 (2.2%)	2 (9.1%)	0.134
Skin rash	12 (3.5%)	12 (3.8%)	0 (0%)	0.354
Myalgia or muscle soreness	22 (6.5%)	21 (6.6%)	1 (4.5%)	0.707

N denotes case number; IQR denotes interquartile range; "duration of fever" is defined as the total duration of fever of the patients. Data are shown as case number (%) or case number/case number (%).

Table 3 Laboratory data of hospitalized children with COVID-19.

	All cases (N = 339)	Nonsevere (N = 317)	Severe (N = 22)	P value
WBC (10^9 cells/L (IQR))	6.44 (4.76–8.56)	6.32 (4.72–8.52)	7.53 (5.20–9.09)	0.187
Leukopenia (% (IQR))	67/327 (20.5%)	63/305 (20.7%)	4/22 (18.2%)	1.000
Segments (% (IQR))	58.6 (39.6–74.2)	56.8 (38.4–73.9)	72.4 (60.9–80.1)	0.003
Neutrophilia	106/325 (32.6%)	94/304 (30.9%)	12/21 (57.1%)	0.013
Platelet count (10^9 cells/L (IQR))	232.5 (187.5–294.5)	233.5 (190.5–296.3)	207.0 (157.0–265.5)	0.090
Thrombocytopenia	37/326 (11.3%)	32/304 (10.5%)	5/22 (22.7%)	0.081
CRP (mg/dL, IQR)	0.270 (0.080–0.750)	0.255 (0.080–0.727)	0.410 (0.070–2.095)	0.213
CRP >1 mg/dL	62/323 (19.2%)	55/302 (18.2%)	7/21 (33.3%)	0.089
Procalcitonin (ng/mL, IQR)	0.1320 (0.0860–0.2650)	0.1265 (0.0860–0.2150)	0.8040 (0.1240–4.2350)	0.002
Procalcitonin >0.5 ng/mL	32/211 (15.2%)	23/194 (11.9%)	9 (52.9%)	<0.001
ALT	17.0 (12.0–26.0)	17.0 (12.0–26.0)	12.5 (9.7–26.2)	0.280
ALT >60 U/L	34/337 (10.1%)	31/315 (9.8%)	3/22 (13.6%)	0.568
Creatinine	0.40 (0.30–0.50)	0.40 (0.30–0.50)	0.45 (0.30–0.65)	0.014
Abnormal creatinine	16 (4.7%)	12 (3.8%)	4 (18.2%)	0.002
Sodium	135 (134–137)	135 (134–136)	136 (133–138)	0.151
Potassium	4.30 (3.90–4.90)	4.30 (3.90–4.90)	4.30 (3.55–4.68)	0.278
LDH	300.0 (250.0–387.5)	304.0 (253.0–394.0)	278.0 (215.0–326.0)	0.185
D-dimer	0.620 (0.400–0.830)	0.670 (0.440–0.830)	0.430 (0.297–0.725)	0.078

N = case number; IQR = interquartile range; CRP = = C-reactive protein; ALT = alanine aminotransferase; LDH = lactate dehydrogenase.

[a] Data are shown as case number (%), number/number (%), or median (interquartile range).

when they were diagnosed with COVID-19, only one with underlying congenital heart disease had preceding endocarditis and sepsis with *Citrobatcer koseri*. The other two patients had methicillin-resistant *Staphylococcus aureus* yielded by sputum cultures, and one patient had *Campylobacter jejuni* yielded by stool culture.

Treatment

Among 339 patients, 95 patients (28.0%) received antiviral agents [90 patients (26.5%) with Remdesivir, and 5 patients (1.5%) with Paxlovid] for COVID-19. Among 96 patients with underlying disease(s), 77 patients (80.2%) received antiviral agent. Among 22 patients with severe COVID-19, 20 patients (90.9%) received antiviral agents. Intravenous immunoglobulin (IVIG) and anti-interleukin-6 (anti-IL6) agent were given in some patients with severe diseases, showed in Supplementary Table S4.

Outcomes

The median duration of hospitalization in all cases was six days (IQR: 4.0—9.0). A longer duration of hospitalization was noted in the severe group (5 days vs. 13.5 days, $p < 0.05$). Among all cases, 26 cases (7.7%) needed increased oxygen supplementation. A higher proportion of patients in the severe group needed increased oxygen supplementation (54.5% vs. 4.4%, $p < 0.001$). The numbers (%) of patients with endotracheal tube intubation, use of inotropic agents, application of extracorporeal membrane oxygenation and death are shown in Table 4.

There were two deaths during hospitalization in our study, and neither patient received antiviral agents within the first five days after COVID-19. One patient with cyanotic congenital heart disease and preceding *Citrobacter koseri* endocarditis received only one dose of remdesivir and died soon after nosocomial SARS-CoV-2 infection. The other patient with multiple congenital anomalies died of ARDS and sepsis syndrome.

Multivariable analysis of clinical predictors of severe COVID-19

The results of multivariable analysis are shown in Table 5. Children with congenital cardiovascular disease (aOR: 21.689; 95% CI: 1.358—346.413), a duration of fever up to four days or more (aOR: 6.466; 95% CI: 1.054—39.673), desaturation (aOR: 16.081; 95% CI: 1.247—207.374) or seizure (aOR: 20.920; 95% CI: 3.149—138.984) and elevated procalcitonin (>0.5 ng/mL) levels (aOR: 7.886; 95% CI: 1.270—48.986) had a significantly higher risk of severe COVID-19.

Discussion

Our study reveals that the underlying disease of congenital cardiovascular diseases, fever duration ≥4 days, desaturation, seizure, and elevated levels of procalcitonin upon admission are the most significant factors associated with severe COVID-19. None of the enrolled patients in our study had previously documented SARS-CoV-2 infection before this admission, and only 8.8% of the included children had received COVID-19 vaccination. These factors may help us be more alert to severe COVID-19 in naïve children infected with Omicron variants of SARS-CoV-2.

The median age of patients with severe COVID-19 (81.5 months) was significantly older than that of patients with nonsevere disease. A similar result was reported by Swann et al.[11] In our study, patients under 1-year-old accounted for 29.8% of the cohort and only 3.9% suffered from severe COVID-19. Ouldali et al. also reported a French cohort in which children younger than 90 days accounted for 37% of cases, but only 3% of them had severe COVID-19.[12] This was different from two studies in China and Italy, which reported a higher rate of severe disease among children

Table 4 Outcomes of hospitalized children with COVID-19.

	All cases (N = 339)	Nonsevere (N = 317)	Severe (N = 22)	P value
Duration of hospitalization (days) (median, IQR)	6.0 (4.0—9.0)	5.0 (4.0—8.0)	13.5 (9.0—34.25)	<0.001
Duration of hospitalization >7 days	108 (31.9%)	90 (28.4%)	18 (81.8%)	<0.001
Need of increased O2 supplements[a]	26 (7.7%)	14 (4.4%)	12 (54.5%)	<0.001
Endotracheal tube intubation and use of mechanical ventilation	11 (3.2%)	0	11 (50.0%)	<0.001
Use of inotropic agent(s)	5 (1.5%)	0	5 (22.7%)	<0.001
Application of extracorporeal membrane oxygenation (ECMO)	1 (0.3%)	0	1 (4.5%)	<0.001
Mortality	2 (0.6%)	0	2 (9.1%)	<0.001

[a] Comparison with the baseline requirement of O2 in individual patients.
IQR denotes interquartile range; N denotes case number.
Data are shown as case numbers (percentages) or medians (interquartile ranges).

Table 5 Multivariable analysis of clinical predictors associated with severe COVID-19 in children.

	Nonsevere (N = 317)	Severe (N = 22)	OR (95% CI)	Adjusted OR (95% CI)
Age >6 years	79 (24.9%)	12 (54.5%)	3.646 (1.517, 8.762)	4.887 (0.804, 29.700)
Cardiovascular disease	11 (3.5%)	4 (18.2%)	6.222 (1.802, 21.483)	21.873 (1.423, 336.326)
Neurological diseases	30 (9.5%)	6 (27.3%)	3.612 (1.315, 9.926)	0.436 (0.026, 7.354)
Multiple underlying diseases[a]	7 (2.2%)	3 (13.6%)	7.038 (1.685, 29.396)	1.501 (0.029, 77.743)
Duration of fever ≥4 days	48 (15.1%)	12 (54.5%)	6.225 (2.545, 15.224)	6.466 (1.054, 39.673)
Rhinorrhea	154 (48.6%)	4 (18.2%)	0.238 (0.079, 0.719)	0.298 (0.040, 2.211)
Cough	224 (70.7%)	8 (36.4%)	0.242 (0.098, 0.597)	0.300 (0.039, 2.313)
Desaturation	12 (3.8%)	7 (31.8%)	11.939 (4.109, 34.686)	16.081 (1.247, 207.374)
Seizure	25 (7.9%)	8 (36.4%)	6.720 (2.573, 17.548)	20.920 (3.149, 138.984)
Neutrophilia	94 (29.7%)	12 (54.5%)	2.979 (1.214, 7.311)	0.643 (0.119, 3.481)
Procalcitonin >0.5 ng/mL	23 (7.3%)	9 (40.9%)	8.364 (2.935, 23.833)	7.886 (1.270, 48.986)
Abnormal creatinine	12 (3.8%)	4 (18.2%)	5.685 (1.666, 19.399)	0.299 (0.020, 4.386)

[a] Underlying condition involves two or more systems.
N denotes case number; OR denotes odds ratio; CI denotes confidence interval.
Data are shown as case number (%), number/number (%), or rate (95% CI).

younger than 1 year and 6 months, respectively.[13,14] In our cohort, most of the hospitalized patients under one year old were admitted due to young infant fever or dehydration but rare severe illness caused by COVID-19.

In the present study, only 6.5% of hospitalized children and adolescents required intensive care. This rate is lower than the rates reported by studies conducted in 2020, which was pre-Omicron wave, in the UK (15%) and in the U.S. (16.7% and 8.7%) in the acute COVID-19 cohort without MIS-C.[11,15,16] In our cohort, only 3.2% of patients needed mechanical ventilation, which was lower than the rate reported by Martin et al. (6% in the acute COVID-19 cohort) and 8.9% reported by Swann et al.[11,17] Adeel et al. also found that Omicron infected children were associated with significantly lower odds of severe disease than Delta infected children.[18] The relatively lower percentage of patients requiring critical care and invasive ventilators may reflect the decreased severity of disease in the Omicron wave.

Patients with comorbidities were significantly more common among patients with severe COVID-19 in our study. A total of 54.5% of patients with severe COVID-19 had underlying diseases, and Swann et al. reported similar results (54.3% of patients with critical care admission).[11] Pediatric patients with comorbidities have been considered a risk factor for severe COVID-19 in many studies.[15,19–21] In our study, we found that congenital cardiovascular disease was the most significant underlying factor of severe COVID-19. Woodruff et al. identified that cardiovascular disease was associated with severe COVID-19 among hospitalized children <2 years but not among patients aged 2–17 years.[6] A cross-sectional study conducted by Kompaniyets et al. showed that cardiac and circulatory congenital anomalies are significant risk factors for severe COVID-19 among patients aged 18 years or younger.[22] Congenital cardiovascular diseases have been considered a risk factor for critical care admission or severe COVID-19 in systematic reviews and meta-analyses conducted by Shi et al. and Choi et al.[15,23]

Most of our patients presented with fever (94.1%), which was higher than data reported in France (74%) and South Africa (61%) during the Omicron wave.[24,25] Most of the patients in our cohort were admitted due to symptomatic SARS-CoV-2 infection, and the two patients with asymptomatic SARS-CoV-2 infection were excluded. The above may be why a high proportion of our patients presented with fever. Another reason is that all patients in our study had no previous SARS-CoV-2 infection, and most did not receive a COVID-19 vaccination. This may result in more patients presenting with symptomatic SARS-CoV-2 infection.[26] We found that fever duration ≥4 days is one factor associated with severe COVID-19. To our knowledge, there have been no previous reports on fever duration associated with severe COVID-19. This finding suggests that we should alert patients about fever duration ≥4 days to be related to developing severe disease, and further survey and management are recommended.

All the 7 patients with severe COVID-19 presenting desaturation had underlying diseases (Supplementary Table S2). These patients were diagnosed as pneumonia with respiratory failure or shock with multiorgan failure. Desaturation may be one of the findings suggesting a decompensated respiratory condition or poor perfusion. Therefore, early management and/or intensive care are recommended in COVID-19 patients with major underlying diseases and desaturation.

Seizure at presentation noted among patients with nonsevere disease was associated with febrile convulsions, underlying disease(s), and encephalopathy. A study in South Africa reported that 20% of hospitalized children aged under 13 years presented with seizures. Most of them were diagnosed with febrile convulsions. Only 16% of them were not in the age range for febrile seizures and had no relevant underlying disease.[25] Encephalopathy was a common manifestation of patients with critically ill COVID-19, which was associated with worse functional outcomes reported by Liotta et al. and Pun et al.[27,28] In our study, seizures at presentation noted in enrolled patients were frequently associated with encephalopathy (15 of 25 patients), and 6 of them required intensive care. As a result, seizure or desaturation at presentation is important manifestations implying potential moderate to severe disease.

We found that an elevated level of procalcitonin (>0.5 ng/mL) upon admission was a factor associated with severe COVID-19 rather than CRP. Procalcitonin is produced from extrathyroidal sources and is inhibited by an increase in

interferon (INF)-γ during viral infection. The biomarker was extremely amplified during bacterial infection.[29] Procalcitonin has been reported as a promising prognostic biomarker of COVID-19 progression in adults in many studies and in a systematic review conducted by Ahmed et al.[29] Compared with adults with COVID-19, abnormal procalcitonin was more common, and higher values of procalcitonin were reported.[30,31] According to a report from Xia et al.,[31] coinfection was common in their cohort, but there was no patient diagnosed with bacteremia or sepsis in our study. Hence, elevated procalcitonin should be taken as a predictor of potential severe COVID-19 irrespective of bacterial coinfection.

There were two deaths in the hospital due to severe COVID-19. Both patients had underlying diseases (cyanotic congenital heart disease and multiple congenital anomalies with epilepsy) but did not receive antiviral agents within the first five days of the onset of illness. Remdesivir, an antiviral agent for SARS-CoV-2 infection that can be applied to pediatric patients, has been identified as having an effect against death or progression to ventilation.[32] Hence, antiviral agents may be considered in patients with high-risk underlying diseases when they are infected by SARS-CoV-2.

The main strength of our study was that all the enrolled patients had no documented previous SARS-CoV-2 infection, and most did not receive a COVID-19 vaccination before they were infected. These points make the analyses less affected by the potential effect of previous infection and/or vaccination. Our study also has several limitations. First, there may be bias due to the small number of patients, especially the small number of severe COVID-19 cases and mortality in children. Second, the demographic characteristics and clinical spectrum of hospitalized patients may be affected by the strategy of disease control and medical resource allocation in different stages of the pandemic. Third, due to the nature of retrospective studies, some laboratory data may be missing or unavailable, which may underestimate their predictive power for severe disease. In addition, our analysis did not include data on radiologic findings that may be potentially associated with severe disease.[33,34] Some previously reported risk factors, including prematurity, obesity, and diabetes,[15,23] were not present in our analysis due to incomplete data or the small number of cases.

In conclusion, this study showed that pediatric patients with cardiovascular disease, fever duration $\geq$4 days, desaturation, or seizure on admission, and procalcitonin $>$0.5 ng/mL were associated with severe COVID-19. When clinicians approach patients with the above conditions, their vital signs, respiratory patterns, neurologic symptoms and activities need close monitoring, early management and/or intensive care may be applied.

Conflicts of interest

None of the authors declare conflicts of interest associated with this manuscript.

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Appendix A. Supplementary data

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