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Short Communication

Clinical outcomes of pediatric COVID-19 in a tertiary care center in Bangkok, Thailand

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ABSTRACT

Objective: To describe the clinical characteristics and outcomes of pediatric COVID-19 in Thailand, where favipiravir is the mainstay of antiviral treatment.

Methods: We conducted a hospital based observational cohort study of COVID-19 among children. The study included children (age <15 years) with confirmed positive reverse transcriptase-polymerase chain reaction for SARS-CoV-2 from nasopharyngeal swab.

Results: From April to July 2021, 416 cases with a median age of 7.1 (interquartile range 2.7–11.6) years were included in the study. The spectrum of disease included 82 (20%) asymptomatic, 232 (56%) mild and 102 (24%) with pneumonia. Abnormal chest x-ray findings included ground-glass opacities (46%), focal infiltrations (27%), perihilar opacities (19%), reticular infiltrations (15%) and other non-specific findings (4%). Only 12 children (3%) required oxygen support. Favipiravir was prescribed to 129 children (31%); 102 patients with pneumonia and 27 patients at risk for disease progression. Pneumonia was more common in age <3 years compared with those aged 3–<12 years (adjusted odds ratio (aOR) 0.30, 95% CI 0.17–0.52), 12–15 years (aOR 0.40, 95% CI 0.21–0.77) and in patients with comorbidities (aOR 2.36, 95% CI 1.09–5.12).

Conclusions: One-fourth of pediatric COVID-19 patients had pneumonia, but few required oxygen support. Off-label use of Favipiravir in pediatric COVID-19 patients in a recent outbreak in Bangkok is reported.

Since December 2019, COVID-19 caused by SARS-CoV-2 has emerged and spread globally. Although children usually have milder disease than adults, the proportion of infected children is increasing (Ludvigsson et al., 2020). In the US, children accounted for 10% of cases in 2020, increasing to 15% in 2021 (Pediatrics AAP, 2021). Data on clinical outcomes of pediatric COVID-19 cases in Asia are limited. In Thailand, the third outbreak resurged in April 2021, coinciding with an increasing proportion of the Delta variant, which is more transmissible and might cause more severe illness. The percentage of Delta variant in Bangkok increased from 22.5% in April to 86.2% in July (Ministry of Public Health, Thailand, 2021).

According to the Thai National Treatment Guidelines for COVID-19 Ministry of Public Health, 2021, favipiravir, a nucleotide analog targeting the viral RNA-dependent RNA polymerase (Delang et al., 2018), is the treatment option for patients at risk of developing severe disease and mild severity of pneumonia. Remdesivir is recommended only for severe disease due to limited access. In addition, anti-SARS-CoV-2 monoclonal antibodies were not available during the study period. The objectives of this study were to describe the clinical characteristics of pediatric COVID-19 cases, assess factors associated with pneumonia and report experiences of favipiravir use in children.

The study was an observational cohort of confirmed COVID-19 patients aged <15 years in a tertiary care center, King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand, from April to July 2021. The KCMH is a 1500-bed tertiary care hospital that collaborates with the Thai Red Cross Emerging Infectious Diseases (EID) Clinical Center, the country's largest EID clinic. At the time of the study, all confirmed COVID-19 cases had to be hospitalized for isolation and COVID-19 vaccines were not available for children. Inclusion criteria for the study were hospitalized patients aged <15 years who had positive reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2. All hospitalized confirmed cases underwent chest x-ray re-

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Table 1
Characteristics of 416 pediatric confirmed COVID-19 cases

Characteristics	All (N=416)	Non-pneumonia (n=314)	Pneumonia (n=102)	*P*-value
Gender				
Male, n (%)	225 (54%)	167 (53%)	58 (57%)	0.517
Ethnicity				0.341
Thai	377 (91%)	287 (91%)	90 (88%)	
Non-Thai	39 (9%)	27 (9%)	12 (12%)	
Median (IQR) age, years	7.1 (2.7–11.6)	7.4 (3.3–11.7)	4.9 (1.6–11.1)	0.014†
Age, years				<0.001
0–<3	113 (27%)	69 (22%)	44 (43%)	
3–<12	208 (50%)	172 (55%)	6 (35%)	
12–15	95 (23%)	73 (23%)	22 (22%)	
Age <1 year	42 (10%)	25 (8%)	17 (17%)	0.011
Month of diagnosis				0.013
April	52 (12%)	48 (15%)	4 (3.9%)	
May	115 (28%)	89 (28%)	26 (25%)	
June	97 (23%)	69 (22%)	28 (27%)	
July	152 (37%)	108 (34%)	44 (43%)	
Comorbidities				
Yes	37 (9%)	22 (7%)	15 (15%)	0.018
Co-morbidities				
Pulmonary diseases	14 (3.4%)	9 (2.9%)	5 (4.9%)	0.322
Hematologic diseases	8 (1.9%)	5 (1.6%)	3 (2.9%)	0.389
Neurological diseases	5 (1.2%)	2 (0.6%)	3 (2.9%)	0.064
Genetic diseases	4 (1.0%)	0 (0.0%)	4 (3.9%)	<0.001
Obesity	9 (2.2%)	3 (1.0%)	6 (5.9%)	0.003
Direct contact with confirmed COVID-19 case				0.844
Household contacts	377 (90.6%)	286 (91.1%)	91 (89.2%)	
Non-household contacts	22 (5.3%)	16 (5.1%)	6 (5.9%)	
No	17 (4.1%)	12 (3.8%)	5 (4.9%)	
Median (IQR) of cycle threshold of RT-PCR SARS-CoV-2	21.6 (17.2-28.2)	21.6 (17.4-28.3)	21.5 (16.3-27.9)	0.564†

IQR; interquartile range, RT-PCR; reverse transcriptase-polymerase chain reaction
P-value calculated by Chi-square test or Fisher exact test as appropriate except † by Mann-Whitney U test

gardless of symptoms. Basic laboratory tests, such as complete blood counts, were performed only if clinically indicated. COVID-19 severity was classified as 1) asymptomatic infections; 2) mild: upper respiratory tract infection or mild other symptoms; 3) moderate: pneumonia either with clinically or abnormal radiological findings; 4) severe: pneumonia with desaturation or need for respiratory support: 5) critical: respiratory failure or life-threatening conditions (Dong et al., 2020). To consider factors associated with pneumonia, we grouped the asymptomatic and mild classifications to a non-pneumonia subgroup and moderate, severe and critical classifications to a pneumonia subgroup. The Thai guidelines recommended favipiravir 35 mg/kg/dose twice daily on day 1, then 15 mg/kg/dose twice daily on days 2–5. Corticosteroid and dexamethasone 0.15 mg/kg/dose once daily were prescribed for up to 5–10 days in COVID-19 patients who required supplemental oxygen or in patients with persistent fever during the inflammatory phase.

Study data were collected and managed using Research Electronic Data Capture (REDCap) Project REDCap Vanderbilt University, 2023. Baseline characteristics were reported as mean (SD) or median (interquartile range, IQR) for continuous variables. Categorical data were constructed using frequencies and percentages. Chi-square test or Fisher's exact test were used to compare categorical variables as appropriate and Mann-Whitney U test to compare continuous variables. Factors associated with pneumonia cases were analyzed using logistic regression. Multivariable models were developed by adjusting for covariates with $P<0.10$ in univariable models. All *P*-values reported were two-sided. Statistical significance was defined as $P<0.05$. Statistical analysis was performed using Stata version 15.1 (Stata Corp., College Station, Texas).

From April to July 2021, there were 416 pediatric confirmed COVID-19 cases. The median age was 7.1 (IQR 2.7–11.6) years, and 42 (10%) cases were <1 year old. Thirty-seven (9%) patients had underlying conditions. Most patients (377, 91%) contacted confirmed COVID-19 cases in household members. Characteristics of confirmed COVID-19 cases are shown in Table 1. There were 82 (20%) asymptomatic infections, 232 (56%) mild, 90 (21%) moderate, 12 (3%) severe and no critical cases.

Grouping asymptomatic and mild cases resulted in 314 patients in the non-pneumonia subgroup, and grouping moderate, severe and critical cases resulted in 102 patients in the pneumonia subgroup. The median age in the pneumonia subgroup was significantly younger than the non-pneumonia subgroup, 4.9 vs 7.4 years ($P=0.014$). The proportion of patients with underlying conditions was significantly higher in the pneumonia subgroup, 15% vs 7% ($P=0.018$) (Table 1). Patients aged 3–<12 years and 12–15 years had a reduced risk of having pneumonia by 70% and 60%, respectively, compared with those aged <3 years. Patients with comorbidities had a higher risk of pneumonia (aOR=2.36, 95% CI 1.09–5.12). We also found that rates of pneumonia significantly increased from April to July 2021 ($P=0.008$) (Supplementary Material). Another factor associated with an increased risk of pneumonia was obesity (Table 2)

Chest x-rays were performed in 410 patients; 94 (23%) had abnormal findings, including 46% with ground glass opacities, 27% focal infiltrations, 19% perihilar opacities, 15% reticular infiltrations and 4% other non-specific findings. Regarding specific treatment, 129 (31%) patients received favipiravir, consisting of 102 pneumonia cases and 27 patients with risk factors for severe disease, e.g., comorbidities, <1 year old. Among the 129 patients who received favipiravir, 120 (93%) had no fever after 72 hours of treatment. None had drug discontinuation due to adverse side effects. Only 3 (0.7%) received remdesivir, 2 due to gastrointestinal tract absorption problems, and 1 immunocompromised patient who had persistent fever after receiving favipiravir for 48 hours. Steroids were prescribed in 13 patients (3.2%). No patients received an anticoagulant. Twelve children (2.9%) required oxygen support; none required invasive ventilation.

Table 2
Adjusted odds ratios of COVID-19 pneumonia among hospitalized patients aged less than 15 years

Characteristics	Univariate OR (95% CI)	*P*-value	Multivariate adjusted OR (95% CI)	*P*-value*
Sex		0.517		
Male	1.16 (0.74–1.82)			
Female	reference			
Ethnicity		0.352		
Thai	0.71 (0.34–1.45)			
Non-Thai	reference			
Age (years)		<0.001		<0.001
<3 years	reference		reference	
3–<12 years	0.33 (0.19–0.55)		0.30 (0.17–0.52)	
≥12 years	0.47 (0.26–0.87)		0.40 (0.21–0.77)	
Month of diagnosis		0.005		0.008
April	reference		reference	
May	3.51 (1.16–10.63)		4.17 (1.32–13.16)	
June	4.87 (1.60–14.78)		5.51 (1.74–17.39)	
July	4.89 (1.66–14.38)		4.51 (1.47–13.83)	
Comorbidities		0.024		0.033
Yes	2.29 (1.14–4.60)		2.36 (1.09–5.12)	
No	reference		reference	
Obesity		0.007		0.015
Yes	6.48 (1.59–26.4)		5.84 (1.35–25.29)	
No	reference		reference	

P-values were analyzed using logistic regression. Multivariable models were developed by adjusting for covariates with $P<0.10$ in the univariable model.

Our study describes the clinical data and outcomes of confirmed pediatric COVID-19 cases in the context of a tertiary care center in a recent outbreak in Bangkok. We observed an increased proportion of symptomatic infection and pneumonia cases from April to July 2021, which may be explained by the Delta variant becoming the dominant strain in the setting. In a US study, increased COVID-19-associated hospitalization rates were potentially due to increased community SARS-CoV-2 transmission or disease severity caused by the Delta variant (Delahoy et al., 2021). Children usually have mild COVID-19 symptoms, but severe cases are found in children of a younger age, obese or with comorbidities. These findings were also described in the pediatric COVID-19 cohort in the US study. Medical personnel should apply this knowledge to early recognition and improve treatment outcomes (Martin et al., 2021).

In Turkey, where drug availability is also limited, favipiravir is recommended for severe pediatric COVID-19 cases. Ozsurekci reported favipiravir use in pediatric patients with renal impairment and showed it was well tolerated without major side effects (Ozsurekci et al., 2021). Favipiravir is not approved for COVID-19 due to the lack of proven efficacy. However, in the US, there is an ongoing phase 3 study of favipiravir for adults with mild to moderate COVID-19 symptoms, which expects to report results by 2021 (Appili Therapeutics, 2021). Here we reported the experience of using favipiravir as a therapeutic option in children due to limited drug availability of approved antiviral agents.

The strength of this study is that it reports on clinical data and outcomes of pediatric COVID-19 confirmed by RT-PCR. To the best of our knowledge, there are few reports on clinical data and outcomes in pediatric COVID-19 cases in developing countries and Asia. Our study also had some limitations. First, data on the SARS-CoV-2 strain and viral clearance after treatment were not confirmed in the study. Our assumption that the Delta variant may be the cause of more severe disease in the later month of the study is uncertain. Overload of cases in the health system also leads to delay in treatment and may affect severity. Additionally, data on further follow-up for post-COVID syndrome and multisystem inflammatory syndrome in children (MIS-C) are needed in the future. In conclusion, one-fourth of hospitalized pediatric COVID-19 cases developed pneumonia, but few required oxygen support. Off-label use of Favipiravir in pediatric COVID-19 patients in a recent outbreak in Bangkok is reported.

Declaration of Competing Interest

The authors declare no conflict of interest

Ethical approval

This study was approved by the Faculty of Medicine, Chulalongkorn University.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2021.11.003.

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