PREDICTORS OF CORONAVIRUS DISEASE 2019 (COVID-19) AMONG PEDIATRIC PATIENTS AT A NATIONAL INFECTIOUS DISEASES HOSPITAL, THAILAND

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Abstract. Children are at risk of contracting SARS-CoV-2, but data on risk factors for coronavirus disease 2019 (COVID-19) among children are limited and inconsistent. In order to determine predictors of COVID-19 among pediatric patients under investigation (PUIs), a retrospective analysis was carried at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand between March 2020 and April 2021 of pediatric patients under 15 years of age who met the national case definition of PUIs for COVID-19 and required medical attention. Nasopharyngeal and oropharyngeal swabs of pediatric PUIs (n = 165; 60% male, median (interquartile range) age = 3 (1-8) years) were subjected to SARS-CoV-2 RT-qPCR assay. Demographic, clinical, laboratory, and radiographic characteristics were compared between RT-qPCR positives (n = 18, 11%) and negatives (n = 147, 89%). Predictors of COVID-19 determined using a multiple logistic regression analysis revealed presence of COVID-19 cases in household (adjusted odds ratio (aOR) = 12.32, 95% confidence interval (CI): 3.87-39.26, p-value <0.001) and body temperature <37.5°C (aOR = 5.48, 95% CI: 1.03-29.27; p-value = 0.047) were independent risk factors for COVID-19 among pediatric PUIs. As this was a cross-sectional study conducted at one site, a multi-center study involving a larger cohort of patients will be needed to validate the findings.

Keywords: COVID-19, patient under investigation, pediatric, predictor, Thailand

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INTRODUCTION

Infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei Province, PR China in December 2019, became a local epidemic but soon spread beyond its borders, with Thailand being the first country outside China with an imported COVID-19 case (Triukose *et al*, 2021). On 11 March 2020, the World Health Organization (WHO) declared the infection a pandemic and named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19) (WHO, 2020b). Subsequently, the Ministry of Public Health (MOPH), Thailand developed a case definition of patients under investigation (PUIs) for COVID-19 based on clinical and epidemiological criteria consistent with the United States Centers for Disease Control and Prevention (CDC) guidelines (Bruminhent *et al*, 2020).

COVID-19 in children has a broad spectrum of diseases ranging from asymptomatic infection, upper respiratory infection, pneumonia, or even death, but in general is less severe than in adults (Bellino *et al*, 2020; National Health Commission, 2020), thus posing a challenge in distinguishing between COVID-19 and other common pediatric illnesses, particularly acute respiratory infection. To date, there are limited data globally on the efficacy and safety of available COVID-19 vaccines in children (Nagakumar *et al*, 2021). In addition, protecting young children against COVID-19 is extremely difficult due to their limited self-independence and inability to wear the facemask (WHO, 2020c). As a result, children remain at risk of contracting SARS-CoV-2, especially if their close contacts have COVID-19.

Only a few studies have been conducted to determine the risk factors of COVID-19 in children, and findings are inconsistent among studies (Murillo-Zamora *et al*, 2020; Arslan *et al*, 2021). Here, predictors of COVID-19 among pediatric PUIs at a national infectious diseases hospital in Thailand were determined using history, physical examination, routine laboratory testing, and chest radiographic data to facilitate early identification, isolation, and prompt treatment, thereby enabling effective allocation of medical resources, a particular necessity in low- and middle-income developing countries.

MATERIALS AND METHODS

Study population and design

We performed a retrospective analysis from March 2020 to April 2021 of pediatric patients under 15 years of age who met the Thai national case definition of PUIs for COVID-19 requiring medical attention at the Bamrasnaradura Infectious Diseases Institute (BIDI), a designated national hospital for emerging infectious diseases in Thailand. The medical histories of pediatric COVID-19 PUIs were retrieved from the database of BIDI epidemiological unit. All pediatric patients who

sought medical attention at BIDI had been assessed for PUI case definition by triage nurses and validated by epidemiologists (see below). Further consultation with attending pediatric infectious diseases specialists was sought in asymptomatic cases who had close contact with persons suspected of or confirmed with COVID-19 to assess the risk of contracting SARS-CoV-2. Findings of the SARS-CoV-2 RT quantitative (q)-PCR assay of nasopharyngeal and oropharyngeal swabs from PUIs requiring hospitalization in isolation rooms for disease containment were retrieved. Patients were monitored daily until discharge. Patients with incomplete medical records were not included in the study.

The research protocols were approved by BIDI Institutional Review Board (approval no. S022h/63 ExPD). Prior written consent was not required as names of the patients were redacted.

PUI case definition

The national case definition of PUI for COVID-19 as published by the Department of Disease Control, MOPH, Thailand on 2 March 2020 (Department of Disease Control, 2020) was followed: (i) patient with any of the following symptoms, *ie* history of fever or body temperature ≥37.5°C, or development of respiratory symptoms, such as cough, rhinorrhea, sore throat, anosmia, ageusia, tachypnea, shortness of breath, or difficulty breathing, in the 14 days preceding onset of symptoms along with risk factors of COVID-19 acquisition, namely, (a) traveled to/from, contacted people who traveled to/from, or resided in countries or areas with ongoing COVID-19 transmission; (b) with risk occupation, such as working in crowded place, closed space, or in close contact with tourists; (c) close contact with suspected or confirmed COVID-19 individual without wearing appropriate personal protective equipment; or (d) high-risk community exposure, such as visiting crowded place or closed space (*eg* market, school, public transportation) as announced by Provincial Communicable Diseases Committee; (ii) pneumonia that was (a) severe, (b) with etiology undetermined within 48-72 hours, or (c) suspected of being COVID-19 as diagnosed by an attending physician; and (iii) cluster (≥5 cases) of acute respiratory infection in the same place within a week that had an epidemiological linkage.

Data collection

Data on epidemiologic, clinical, laboratory, and chest radiographic findings from the first day of admission (unless indicated otherwise), along with clinical classification and outcomes data, were collected from BIDI medical records. The highest temperature was defined as the highest recorded axillary temperature measured during hospitalization, and the minimum oxygen saturation was the lowest recorded oxygen saturation measured by a pulse oximeter (SpO_2) during

hospitalization. RT-qPCR testing was done in all patients, and then the patients were categorized into two groups, COVID-19 and non-COVID-19, according to their SARS-CoV-2 RT-qPCR results. Initial investigations included chest radiograph and complete blood count (CBC), with relative lymphocytosis defined as percent lymphocyte >40%.

Clinical classification

Clinical classification was divided into three categories according to diagnosis upon discharge, namely, asymptomatic, acute respiratory infection (ARI), and non-ARI. ARI group was further classified according to WHO (2020a) guidelines on COVID-19 into (a) upper respiratory tract infection; (b) non-severe pneumonia (cough or difficulty in breathing, accompanied by rapid breathing (≥60, ≥50, ≥40, and ≥30 breath/minute for <2 months, 2-11 months, 12 months-5 years, and >5 years of age, respectively), and no signs of severe pneumonia; (c) severe pneumonia (cough or difficulty in breathing, in addition to more than one of the following: central cyanosis or SpO_2 <90%, severe respiratory distress (*eg* grunting or very severe chest indrawing), signs of pneumonia with any general danger sign, namely, inability to breastfeed or drink, lethargy or unconsciousness, or convulsion; and (d) critical case (acute respiratory distress syndrome, shock, sepsis, septic shock, or multiple organ failure). Non-ARI patients were classified based on the discharge diagnosis.

Statistical analysis

Data are presented as frequency, mean ± standard deviation (SD), or median and interquartile range (IQR). Categorical variables were compared using a Chi-square test or Fisher's exact test. Continuous variables were compared using Student's t-test for normally distributed data and Mann-Whitney U test for skewed data. Multiple logistic regression analysis was carried out to determine predictors of COVID-19 among pediatric PUIs for COVID-19. Variables with p-value <0.05 in univariate analysis were included in multivariate analysis after assessment of multicollinearity. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA/IC for Windows, version 15.1 (StataCorp, College Station, TX).

RESULTS

Of pediatric patients (n = 655) who underwent SARS-CoV-2 RT-qPCR at BIDI, Nonthaburi Province from March 2020 to April 2021, 165 patients met the case definition of PUIs for COVID-19, had a median (IQR) age of 3 (1-8) years, 60% were male and 96% of Thai citizenship (Table 1). SARS-CoV-2 RT-qPCR confirmed 11% of PUIs had COVID-19, among whom only one (6%) presented a comorbidity (immunocompromised status), while among non-COVID-19 PUIs, 16% presented comorbidities. There were no significant differences between the two groups in terms of gender proportion,

Table 1

Baseline characteristics of pediatric patients under investigation for COVID-19 at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand (March 2020 - April 2021)

Characteristic	Total (n = 165) Number (%)	COVID-19 (n = 18) Number (%)	Non-COVID-19 (n = 147) Number (%)	p-value*
Male	99 (60)	11 (61)	88 (60)	0.919
Age in years, median (IQR)	3 (1-8)	7 (1-11)	3 (1-8)	0.192
Age distribution in year(s)				
<1	29 (18)	3 (16)	26 (18)	0.211
1-5	77 (46)	5 (28)	72 (49)	
6-10	34 (21)	5 (28)	29 (20)	
11-15	25 (15)	5 (28)	20 (13)	
Nationality				
Thai	158 (96)	17 (94)	141 (97)	0.226
Burmese	2 (1)	0	2 (1)	
Cambodian	2 (1)	0	2 (1)	
British	2 (1)	0	2 (1)	
Guinean	1 (1)	1 (6)	0	

Table 1 (cont)

Characteristic	Total (n = 165) Number (%)	COVID-19 (n = 18) Number (%)	Non-COVID-19 (n = 147) Number (%)	p-value*
Comorbidity				
None	140 (84)	17 (94)	123 (83)	0.467
Immunosuppression	4 (2)	1 (6)	3 (2)	
Asthma	3 (2)	0	3 (2)	
Neurological disease	1 (1)	0	1 (1)	
Morbid obesity	1 (1)	0	1 (1)	
Others†	16 (10)	0	16 (11)	

*Significant if <0.05; †Allergic rhinitis (n = 8), anemia (n = 2), glucose-6-phosphate dehydrogenase deficiency (n = 2), adenotonsillar hypertrophy (n = 1), congenital hydronephrosis (n = 1), and short bowel syndrome (n = 1)

IQR: interquartile range

median age (although the non-COVID-19 group had a lower median value), age distribution, and nationality (~95% Thai).

COVID-19 PUIs had a history of significantly more contacts with household members with COVID-19 (Table 2). Surprisingly, among the non-COVID-19 PUIs, 60% had a history of exposure to a high-risk community. At admission, one-third of COVID-19 PUIs (n = 6) were asymptomatic compared to 2% (n = 3) in the non-COVID-19 group (Table 3). Symptoms in both groups included fever or body temperature ≥37.5°C and/or respiratory problems. The CBC profile did not reveal significant differences between the two groups, with the exception of percent lymphocytes and relative lymphocytosis, which were significantly higher, and percent neutrophils, which was significantly lower in the COVID-19 group. Among the PUIs whose chest radiograph results were available, those in the COVID-19 group did not present significantly more chest abnormalities, except for two patients (11%) in the COVID-19 group with ground-glass opacity compared to one (1%) in the non-COVID-19 group, and two in the non-COVID-19 group (1%) with pleural effusion and none, to be expected due to the low prevalence, in the COVID-19 group.

During hospitalization at BIDI, COVID-19 compared to non-COVID-19 PUIs had significantly less frequent fever episodes, lower median peak (37.4 *vs* 38.9°C) and lower maximum (<37.5 *vs* 39.0°C) body temperature, and were less likely to present gastrointestinal symptoms, including nausea/vomiting, diarrhea, and abdominal pain (Table 3). Anosmia and ageusia were not found.

During the period of admission at BIDI, in terms of clinical classification, more COVID-19 compared to non-COVID-19 PUIs presented with non-severe pneumonia (39 *vs* 18%) and asymptomatic SARS-CoV-2 infection (22 *vs* 2%) (Table 4). There were no cases with severe or critically ill COVID-19. The majority of non-COVID-19 patients (75%) were diagnosed with acute respiratory infection, primarily of the upper respiratory tract (54%), followed by acute gastrointestinal infection (9%). Diarrhea was the most frequently encountered complication in both groups, but there were no statistically significant differences in terms of complications or outcomes between the two groups (Table 4).

Univariate analysis was carried out to identify factors significantly associated with COVID-19 PUIs (p-value <0.05), these being a history of contact with household members with COVID-19 and, at admission, absence of fever, body temperature <37.5°C, absence of gastrointestinal symptoms, lower percent neutrophils, higher percent lymphocytes, and relative lymphocytosis (Table 5). Multivariate analysis was then used to identify independent factors, revealing a history of contact with household members with COVID-19 and a body temperature <37.5°C at the time of admission as predictors of COVID-19.

Table 2

History of pediatric patients under investigation (PUIs) for COVID-19 upon admission at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand (March 2020 - April 2021)

History	Number of confirmed COVID-19[a] (%) (n = 18)	Number of confirmed non-COVID-19[a] (%) (n = 147)	p-value*
Asymptomatic and had close contact with suspected or confirmed COVID-19 individual(s) in the previous 14 days	6 (33)	3 (2)	<0.001
Symptomatic[b] and in the 14 days prior to symptom onset had			
Contact with suspected or confirmed COVID-19 individual(s)	12 (67)	17 (12)	<0.001
Exposure to household occupation risk[c]	4 (22)	52 (35)	0.266
Exposure to high-risk community[d]	0	89 (60)	NA
Traveled to/from or resided in countries/areas with ongoing COVID-19 transmission	0	14 (9)	NA
Contact with individual(s) who traveled to/from or resided in countries/areas with ongoing COVID-19 transmission	0	3 (2)	NA
Pneumonia			
of unknown etiology or did not respond to treatment within 48-72 hours	0	4 (3)	NA
Compatible with COVID-19	0	1 (1)	NA
Cluster of acute respiratory infection[e]	0	1 (1)	NA

Table 2 (cont)

History	Number of confirmed COVID-19[a] (%) (n = 18)	Number of confirmed non-COVID-19[a] (%) (n = 147)	p-value*
Contact with confirmed COVID-19 case(s)	18 (100)	16 (11)	<0.001
In household	17 (94)	10 (7)	<0.001
of 1 case	8 (44)	7 (5)	<0.001
of 2 cases	7 (39)	3 (2)	<0.001
>2 cases	2 (11)	0	<0.001
From parental workplace	1 (6)	8 (5)	0.984
Animal exposure	0	2 (1)	NA

*Significant if <0.05

[a]SARS-CoV-2 RT-qPCR; [b]With any of the following symptoms: history of fever or body temperature ≥37.5°C, or developed any respiratory symptoms, such ageusia, anosmia, cough, difficulty in breathing, rhinorrhea, shortness of breath, sore throat, or tachypnea; [c]Worked in crowded place or closed space, or had close contact with tourists; [d]Visited crowded places or closed spaces (*eg* market, school, and public transportation) as announced by Provincial Communicable Diseases Committee; [e]≥5 cases within a week, which have an epidemiological linkage

NA: not applicable

Table 3

Clinical characteristics of pediatric patients under investigation for COVID-19 upon admission at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand (March 2020 - April 2021)

Characteristic	COVID-19 (n = 18) Number (%)	Non-COVID-19 (n = 147) Number (%)	p-value*
Symptom			
Asymptomatic	6 (33)	3 (2)	<0.001
Fever	9 (50)	131 (89)	<0.001
Respiratory symptom	11 (61)	118 (80)	0.063
Cough	7 (39)	82 (56)	0.175
Nasal congestion/rhinorrhea	7 (39)	74 (50)	0.359
Sore throat	2 (11)	35 (24)	0.223
Dyspnea	1 (6)	20 (14)	0.333
Tachypnea	1 (6)	14 (9)	0.580
Gastrointestinal symptom	2 (11)	56 (38)	0.024
Nausea/vomiting	2 (11)	40 (27)	0.139
Diarrhea	0	25 (17)	0.058
Abdominal pain	0	2 (1)	0.619
Other	3 (17)	34 (23)	0.535
Headache	1 (6)	24 (16)	0.229
Myalgia	1 (6)	6 (4)	0.770
Rash	1 (6)	9 (6)	0.924
Combined respiratory and gastrointestinal symptoms	2 (11)	39 (26)	0.153
Duration between symptom onset and testing[a] (days), median (IQR)	2 (1-4)	1 (1-2)	0.112

Table 3 (cont)

Characteristic	COVID-19 (n = 18) Number (%)	Non-COVID-19 (n = 147) Number (%)	p-value*
Physical examination			
Highest temperature (°C), median (IQR)	37.4 (37.1-37.7)	38.9 (37.9-39.6)	<0.001
Highest temperature range			
<37.5°C	12 (66)	21 (14)	<0.001
37.5-37.9°C	3 (17)	16 (11)	0.468
38.0-38.9°C	3 (17)	38 (26)	0.395
≥39°C	0	71 (48)	<0.001
Tachypnea[b]	1 (6)	8 (5)	0.984
Minimum SpO_2 (%), mean ± SD	97.4 ± 0.9	98.0 ± 1.6	0.143
≥96	18 (100)	141 (96)	0.383
<96	0	6 (4)	0.383
Breath sound			
Normal	17 (94)	128 (87)	0.366
Rhonchi	1 (6)	12 (8)	0.698
Crepitation	0	4 (3)	0.479
Wheezing	0	3 (2)	0.541
Complete blood count	12 (67)	142 (97)	
Hemoglobin (g/dl), median (IQR)	12.8 (12.0-13.6)	12.2 (11.4-12.8)	0.072
White blood cell count, $\times 10^9$ cells/l, median (IQR)	8.0 (6.0–12.7)	10.3 (7.9–14.7)	0.155
Neutrophil, %, median (IQR)	40.0 (22.0-51.5)	61.5 (49.0-76.0)	<0.001
Lymphocyte, %, median (IQR)	49.5 (40.0-66.0)	29.0 (16.0-40.0)	0.001
Relative lymphocytosis[c]	15 (83)	40 (27)	<0.001
Platelet count, $\times 10^9$ cells/l, median (IQR)	310 (287-396)	282 (242-357)	0.148

Table 3 (cont)

Characteristic	COVID-19 (n = 18) Number (%)	Non-COVID-19 (n = 147) Number (%)	p-value*
Chest radiograph	17 (94)	112 (76)	
Normal	3 (17)	31 (21)	0.557
Abnormal	14 (78)	81 (55)	0.557
Thickened lung marking	8 (44)	56 (38)	0.602
Interstitial infiltration	5 (28)	18 (12)	0.073
Ground-glass opacity	2 (11)	1 (1)	0.002
Patchy infiltration	1 (6)	8 (5)	0.984
Pleural effusion	0	2 (1)	NA

*Significant if <0.05

[a]Only symptomatic patients were included in the estimation of median (IQR) duration of symptom onset and testing (12 and 144 patients in COVID-19 and non-COVID-19 group respectively); [b]Abnormal rapid breathing (≥60, ≥50, ≥40, and ≥30 breaths/minute for patients <2 months, 2-11 months, 1 year-5 years, and >5 years of age, respectively); [c]Lymphocyte >40%

g/dl: gram per deciliter; IQR: interquartile range; l: liter; NA: not applicable; SD: standard deviation; SpO_2: oxygen saturation measured using pulse oximeter

DISCUSSION

COVID-19 has a significant impact on a nation's public health and healthcare system, economy and education (Carter *et al*, 2020; Kuhfeld *et al*, 2020). Since March 2020, Thailand has experienced three waves of local COVID-19 outbreaks. The first two waves, occurring in March and December 2020, were confined to communities and did not result in a significant number of children with COVID-19, while the third wave, beginning in April 2021, spread among households, resulting in numerous pediatric COVID-19 cases (Royal College Pediatricians of Thailand, 2021). Our study at a single hospital in Nonthaburi Province, Thailand reflects the COVID-19 situation in the country, with the highest prevalence of pediatric COVID-19 PUIs (80%) and the majority of COVID-19 diagnoses (89%) occurring in April 2021.

Over the one-year study period, COVID-19 prevalence among pediatric PUIs in the study was comparable to previous studies in children, 16% in

Table 4

Clinical classifications, complications and outcomes of pediatric patients under investigation for COVID-19 during admission at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand (March 2020 - April 2021)

Classification, complication and outcome	COVID-19 (n = 18) Number (%)	Non-COVID-19 (n = 147) Number (%)	p-value*
Clinical classification			
Asymptomatic	4 (22)	3 (2)	<0.001
Acute respiratory infection	14 (78)	111 (75)	0.832
Upper respiratory infection	7 (39)	80 (54)	0.213
Non-severe pneumonia	7 (39)	26 (18)	0.034
Severe pneumonia	0	4 (3)	NA
Acute gastrointestinal infection	0	13 (9)	NA
Dengue infection	0	7 (4)	NA
Viral exanthem	0	5 (3)	NA
Febrile convulsion	0	5 (3)	NA
Others	0	7 (4)	NA
Complication and outcome	10 (56)	62 (42)	
Diarrhea	10 (56)	53 (36)	0.108
Sinusitis	0	3 (2)	NA
Required low-flow oxygen therapy	1 (6)	6 (4)	0.770
Required high-flow oxygen therapy	0	2 (1)	NA
Required mechanical ventilation	0	1 (1)	NA
Required ICU admission	1 (6)	3 (2)	0.148
Others	0	4 (3)	NA

*Significant if <0.05

ICU: intensive care unit; IQR: interquartile range; NA: not applicable

Table 5

Logistic regression analysis of factors associated with COVID-19 among pediatric patients under investigation for COVID-19 at Bamrasnaradura Infectious Diseases Institute, Nonthaburi Province, Thailand (March 2020 - April 2021)

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value*	aOR (95% CI)	*p*-value*
Age	1.01 (1.00-1.02)	0.113	-	-
Presence of confirmed COVID-19 cases in households	19.18 (6.60-55.74)	<0.001	12.32 (3.87–39.26)	<0.001
Presenting sign and symptom				
Absence of fever	8.19 (2.84-23.63)	<0.001	-	-
Body temperature <37.5°C	12.00 (4.06-35.46)	<0.001	5.48 (1.03–29.27)	0.047
Absence of respiratory symptoms[a]	2.59 (0.92-7.26)	0.071	-	-
Absence of GI symptoms[b]	4.92 (1.09-22.22)	0.038	1.38 (0.12–16.48)	0.799
Complete blood count				
Hemoglobin	1.35 (0.82-2.21)	0.237	-	-
Percent neutrophil	0.93 (0.90-0.97)	<0.001	-	-
Percent lymphocyte	1.07 (1.03-1.10)	<0.001	-	-
Relative lymphocytosis[c]	13.38 (3.68-48.67)	<0.001	3.52 (0.51–24.11)	0.200

Table 5 (cont)

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value*	aOR (95% CI)	*p*-value*
Chest radiograph				
Abnormality	0.84 (0.67-1.05)	0.124	-	-
Interstitial infiltration	0.86 (0.70-1.05)	0.141	-	-
Ground-glass opacity	0.85 (0.69-1.05)	0.136	-	-

*Significant if <0.05

[a]Cough, dyspnea, nasal congestion/rhinorrhea, sore throat, or tachypnea; [b]Abdominal pain, diarrhea, or nausea/vomiting; [c]Lymphocyte >40%

aOR: adjusted odds ratio; CI: confidence interval; GI: gastrointestinal; OR: odds ratio

Mexico (Murillo-Zamora *et al*, 2020) and in adults, 8-13% in Thailand (Bruminhent *et al*, 2020; Sirijatuphat *et al*, 2021). COVID-19 prevalence is even lower (1-2%) among patients without risk factors (Sastry *et al*, 2020; Alsuhaibani *et al*, 2021). Due to the low prevalence of COVID-19 among children, a targeted approach based on PUI case definition is currently being used in Thailand to identify children at risk of COVID-19 in a hospital setting (Department of Disease Control, 2020). Occasionally, a universal screening is employed during periods of high prevalence, in particular among patients undergoing surgery, procedures involving generation of aerosol, or prior to admission.

As risk factors for contracting SARS-CoV-2 are unclear, a comparative study was undertaken at BIDI over a one-year of sociodemographic factors, previous history of possible contact with risk persons and situations, clinical presentations, and laboratory investigations of pediatric PUIs for COVID-19 at the time of admission. From univariate analysis, factors significantly associated with detection of SARS-CoV-2 infection were subsequently subjected to a multivariate analysis to determine independent factors, namely, history of contact with household member(s) with COVID-19 and a body temperature <37.5°C at the time of admission.

The importance of adult household contacts with COVID-19 as a predictor of pediatric COVID-19 has been reported (Madewell *et al*, 2020; Murillo-Zamora *et al*, 2020; Arslan *et al*, 2021). Conversely, older children and adolescents can also transmit the infection to vulnerable family members, particularly the elderly or those with underlying medical conditions (Chu *et al*, 2021). However, exposure to high-risk communities, which has been reported as a significant source of COVID-19 transmission in adults (Fisher *et al*, 2020), played no significant role in our study because numerous public health and social measures were implemented to mitigate COVID-19 transmission during the study period, including physical distancing, discouragement of unnecessary travel outside home, avoidance of crowded places and closed spaces with poor ventilation, wearing of facemask, regular hand hygiene, and limited in-person learning or school closure (Zhang *et al*, 2020a). However, additional research will be needed to determine the role of high-risk community exposure in SARS-CoV-2 transmission to children following relaxation of mitigation measures.

A precautionary assumption of infection among pediatric PUIs for COVID-19 is a wise step as the majority of children with COVID-19 are asymptomatic or mildly symptomatic (Jiehao *et al*, 2020). We observed one-third of pediatric patients with COVID-19 were asymptomatic at admission. Thus, determination of a history of close contacts with COVID-19 individuals is an important critical

strategy for identifying potential cases of SARS-CoV-2 infection (Bi *et al*, 2020).

We noted a history of fever in approximately half of the children at admission who subsequently were tested positive for SARS-CoV-2 infection. However, among children presenting with symptoms putative of COVID-19, the proportion of those with a history of fever is significantly lower in those who were subsequently tested positive for SARS-CoV-2 than those who were tested negative. Previous studies reported that more than half of children with COVID-19 do not exhibit fever as a presenting symptom, in contrast to adults with COVID-19 (Lu *et al*, 2020; Islam *et al*, 2021). As no pediatric PUIs in the COVID-19 group had a body temperature of 39.0°C, children who present with high-grade fever should be investigated (in addition to COVID-19) for other respiratory viral infections, dengue in tropical regions (Harapan *et al*, 2021; Islam *et al*, 2021) and leptospirosis particularly during floods in the rainy seasons (Li and Bao, 2021).

Gastrointestinal symptoms, in particular nausea and vomiting, abdominal pain, and diarrhea are frequently observed in pediatric COVID19 patients, and occur before, concurrent with, or after development of respiratory symptoms (Akobeng *et al*, 2020; Al-Beltagi *et al*, 2021). We noted approximately half of pediatric COVID-19 patients developed diarrhea during hospitalization rather than at the time of admission.

Pneumonia was present in half of the pediatric COVID-19 cases despite the absence of severe symptoms as similarly reported previously (Qiu *et al*, 2020). Chest radiographs detected abnormalities in up to 78% of the COVID-19 cases, the majority of which were non-specific (Wang *et al*, 2020). Ground-glass opacity is the most common abnormal radiologic finding in COVID-19 (Zhang *et al*, 2020b; Cui *et al*, 2021), but accounting for only 11% in our study.

Regarding laboratory findings, the majority of COVID-19 patients in our study had normal CBC profiles, with the exception of relatively higher percent lymphocytes, lower percent neutrophils, and relative lymphocytosis. Lymphocytes are essential in the host defense mechanism and inflammatory response during SARS-CoV-2 infection, with percent lymphocytes >20% within 10-12 days post-symptom onset in patients with mild to moderate COVID-19 (Azkur *et al*, 2020), similarly observed among the majority of our COVID-19 pediatric patients and was associated with a favorable outcome.

Our study possessed several strengths compared to other similar studies. Firstly, the study was conducted over a one-year period and included patients from communities with both low and moderate COVID-19 transmission. Secondly, we employed data on history, physical examination, laboratory tests, and chest radiography, that are applicable to any hospital to identify predictors of COVID-19 among pediatric PUIs.

And thirdly, patients were monitored daily during their hospitalization. On the other hand, the study also suffered from some limitations: (i) the study was conducted in a single (infectious diseases) hospital and the results do not represent conditions in other hospitals across the country, (ii) COVID-19 pediatric patients with atypical features, such as gastrointestinal, ocular, dermatological, and/or non-specific symptoms, may have been missed by the PUI case definition employed, which is primarily focused on fever and/or respiratory symptoms, (iii) there was a small proportion of patients with comorbidities that increase risk of developing severe COVID-19, and (iv) physical examination data were limited owing to concerns over the contagious nature of SARS-CoV-2.

In conclusion, our study discovers independent predictors of COVID-19 among pediatric patients under investigation were (i) a history of household contacts with COVID-19 and (ii) body temperature <37.5°C at the time of admission. In addition, the national health authorities should update the pediatric PUI case definition for COVID-19 on a regular basis to enable early detection and control of COVID-19 in children.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

Akobeng AK, Grafton-Clarke C, Abdelgadir I, Twum-Barimah E, Gordon M. Gastrointestinal manifestations of COVID-19 in children: a systematic review and meta-analysis. *Frontline Gastroenterol* 2020; 12: 332-7.

Al-Beltagi M, Saeed NK, Bediwy AS, El-Sawaf Y. Paediatric gastrointestinal disorders in SARS-CoV-2 infection: epidemiological and clinical implications. *World J Gastroenterol* 2021; 27: 1716-27.

Alsuhaibani MA, Kobayashi T, Trannel A, *et al*. Coronavirus disease 2019 (COVID-19) admission screening and assessment of infectiousness at an academic medical center in Iowa, 2020, 2021 [cited 2021 Aug 01]. Available from: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8327298/pdf/S0899823X21002944a.pdf

Arslan G, Aktürk H, Duman M. Clinical characteristics of pediatric coronavirus disease 2019 and predictors of polymerase chain reaction positivity, 2021 [cited 2021 Aug 01]. Available from: URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8013810/pdf/PED-9999-0.pdf

Azkur AK, Akdis M, Azkur D, *et al*. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy* 2020; 75: 1564-81.

Bellino S, Punzo O, Rota MC, *et al*. COVID-19 disease severity risk factors for pediatric patients in Italy. *Pediatrics* 2020; 146: e2020009399.

Bi Q, Wu Y, Mei S, *et al*. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis* 2020; 20: 911-9.

Bruminhent J, Ruangsubvilai N, Nabhindhakara J, Ingsathit A, Kiertiburanakul S. Clinical characteristics and risk factors for coronavirus disease 2019 (COVID-19) among patients under investigation in Thailand. *PLoS One* 2020; 15: e0239250.

Carter P, Anderson M, Mossialos E. Health system, public health, and economic implications of managing COVID-19 from a cardiovascular perspective. *Eur Heart J* 2020; 41: 2516-8.

Chu VT, Yousaf AR, Chang K, *et al*. Household transmission of SARS-CoV-2 from children and adolescents. *N Engl J Med* 2021; 385: 954-6.

Cui X, Zhao Z, Zhang T, *et al*. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). *J Med Virol* 2021; 93: 1057-69.

Department of Disease Control. Guidelines for medical practice, diagnosis, treatment and prevention of Healthcare-associated infection in response to patients with COVID-19 infection, 2020 [cited 2020 Apr 01]. Available from: URL: https://ddc.moph.go.th/viralpneumonia/eng/file/guidelines/g_CPG.pdf

Fisher KA, Tenforde MW, Feldstein LR, *et al*. Community and close contact exposures associated with COVID-19 among symptomatic adults ≥18 years in 11 outpatient health care facilities - United States, July 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1258-64.

Harapan H, Ryan M, Yohan B, *et al*. Covid-19 and dengue: double punches for dengue-endemic countries in Asia. *Rev Med Virol* 2021; 31: e2161.

Islam MA, Kundu S, Alam SS, Hossan T, Kamal MA, Hassan RJPo. Prevalence and characteristics of fever in adult and paediatric patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of 17515 patients. *PLoS One* 2021; 16: e0249788.

Jiehao C, Jin X, Daojiong L, *et al*. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020; 71: 1547-51.

Kuhfeld M, Soland J, Tarasawa B, Johnson A, Ruzek E, Liu J. Projecting the potential impact of COVID-19 school closures on academic achievement. *Educ Researcher* 2020; 49: 549-65.

Li B, Bao C. Disparity in clinical characteristics between 2019 novel coronavirus pneumonia and leptospirosis. *Open Med (Wars)* 2021; 16: 494-7.

Lu X, Zhang L, Du H, *et al*. SARS-CoV-2 infection in children. *N Engl J Med* 2020; 382: 1663-5.

Madewell ZJ, Yang Y, Longini IM, Jr, Halloran ME, Dean NE. Household transmission of SARS-CoV-2: a systematic review and meta-analysis. *JAMA Netw Open* 2020; 3: e2031756.

Murillo-Zamora E, Aguilar-Sollano F, Delgado-Enciso I, Hernandez-Suarez CM. Predictors of laboratory-positive COVID-19 in children and teenagers. *Public Health*. 2020; 189: 153-7.

Nagakumar P, Chadwick C-L, Bush A, Gupta A. Collateral impact of COVID-19: why should children continue to suffer? *Eur J Pediatr* 2021; 180: 1975-9.

National Health Commission. Report of the WHO-China Joint Mission on Coronavirus Disease 2019, 2020 [cited 2021 Aug 01]. Available from: URL: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020; 20: 689-96.

Royal College Pediatricians of Thailand. Declaration of COVID-19 situation (2/2021) and COVID-19 vaccination in children, 2021 [cited 2021 Sep 20]. Available from: URL: https://www.thaipediatrics.org/Media/media-20210723054602.pdf [in Thai]

Sastry SR, Pryor R, Raybould JE, *et al*. Universal screening for the SARS-CoV-2 virus on hospital admission in an area with low COVID-19 prevalence. *Infect Control Hosp Epidemiol* 2020; 41: 1231-3.

Sirijatuphat R, Suputtamongkol Y, Angkasekwinai N, *et al*. Epidemiology, clinical characteristics, and treatment outcomes of patients with COVID-19 at Thailand's university-based referral hospital. *BMC Infect Dis* 2021; 21: 382.

Triukose S, Nitinawarat S, Satian P, *et al*. Effects of public health interventions on the epidemiological spread during the first wave of the COVID-19 outbreak in Thailand. *PLoS One* 2021; 16: e0246274.

Wang D, Ju X, Xie F, *et al*. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. *Zhonghua Er Ke Za Zhi* 2020; 58: 269-74.

World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 2020a [cited 2021 May 01]. Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf?sequence=1&isAllowed=y

World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report-51, 2020b [cited 2021 May 01]. Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/331475/nCoVsitrep11Mar2020-eng.pdf?sequence=1&isAllowed=y

World Health Organization (WHO). Mask use in the context of COVID-19: interim guidance, 2020c [cited 2021 May 01]. Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/337199/WHO-2019-nCov-IPC_Masks-2020.5-eng.pdf?sequence=1&isAllowed=y

Zhang J, Litvinova M, Liang Y, *et al*. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. *Science* 2020a; 368: 1481-6.

Zhang JJ, Dong X, Cao YY, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020b; 75: 1730-41.