

Comparative Analysis of Pediatric COVID-19 Infection in Southeast Asia, South Asia, Japan, and China

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Abstract. There is a scarcity of data regarding coronavirus disease 2019 (COVID-19) infection in children from southeast and south Asia. This study aims to identify risk factors for severe COVID-19 disease among children in the region. This is an observational study of children with COVID-19 infection in hospitals contributing data to the Pediatric Acute and Critical Care COVID-19 Registry of Asia. Laboratory-confirmed COVID-19 cases were included in this registry. The primary outcome was severity of COVID-19 infection as defined by the World Health Organization (WHO) (mild, moderate, severe, or critical). Epidemiology, clinical and laboratory features, and outcomes of children with COVID-19 are described. Univariate and multivariable logistic regression models were used to identify risk factors for severe/critical disease. A total of 260 COVID-19 cases from eight hospitals across seven countries (China, Japan, Singapore, Malaysia, Indonesia, India, and Pakistan) were included. The common clinical manifestations were similar across countries: fever (64%), cough (39%), and coryza (23%). Approximately 40% of children were asymptomatic, and overall mortality was 2.3%, with all deaths reported from India and Pakistan. Using the multivariable model, the infant age group, presence of comorbidities, and cough on presentation were associated with severe/critical COVID-19. This epidemiological study of pediatric COVID-19 infection demonstrated similar clinical presentations of COVID-19 in children across Asia. Risk factors for severe disease in children were age younger than 12 months, presence of comorbidities, and cough at presentation. Further studies are needed to determine whether differences in mortality are the result of genetic factors, cultural practices, or environmental exposures.

INTRODUCTION

The infection rates of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are disproportionately low in children compared with adults since its estimated emergence in November 2019. The first pediatric study from the Chinese Center for Disease Control and Prevention ($N = 2,143$) reported a relatively low incidence of severe/critical cases (5.9% among infected cases) and one death.¹ However, severe or critical illness and death among children with coronavirus disease 2019 (COVID-19) can occur. A dedicated report from 46 North American pediatric intensive care units (ICUs) identified 48 critically ill patients with pediatric COVID-19 infection.² The Italian Integrated COVID-19 Surveillance System identified 3,836 children with COVID-19 infection, of which 86 of 3,836 (2.2%) developed severe/critical disease and four (0.1%) died.³ In a meta-analysis of 7,780 pediatric COVID-19 patients, complications such as shock, disseminated coagulopathy, kidney injury, and need for mechanical ventilation occurred in less than 1% and

death in 0.1% of children.⁴ Among the 131 studies identified during this meta-analysis, there was a conspicuous absence of data on COVID-19 in children, especially from southeast and south Asia.⁴ There have also been reports from Europe^{5,6} and the United States⁷ of a Kawasaki-like syndrome affecting children who have recently recovered from COVID-19. This has been termed multisystem inflammatory syndrome in children (MIS-C), and deaths have been reported from this syndrome. However, to date, apart from India⁸ and Pakistan,⁹ no reports of MIS-C have been reported from southeast Asia as well as China, Japan, and South Korea, which may indicate a possible geographic or genetic variation in risk to COVID-19.

This study aims to describe and compare the clinical epidemiology of pediatric COVID-19 infection in southeast Asia (Singapore, Malaysia, and Indonesia), south Asia (India and Pakistan), Japan, and China. We also identify risk factors for severe COVID-19 among children in the region.

MATERIALS AND METHODS

We conducted an observational study of children with COVID-19 infection admitted to hospitals contributing data to the Pediatric Acute and Critical Care COVID-19 Registry of Asia (PACCOVRA). This is an ongoing registry (www.clinicaltrials.gov)

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registration no. NCT04395781) within the Pediatric Acute and Critical Care Asian Medicine Network. Characteristics of participating centers have been described elsewhere.¹⁰ Reporting was conducted in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹¹ Institutional review board approval was obtained from all participating hospitals, and waiver of consent was granted at all sites.

Patients. Patients were identified through administrative databases or hospital admission logs of suspected/confirmed COVID-19 cases. A subset of the cases ($n = 70$) from Singapore¹² and India were published previously.¹³ All infants and children from birth to 21 years at the time of diagnosis were included. A confirmed COVID-19 case was defined as a patient with laboratory confirmation of SARS-CoV-2 infection. Laboratory confirmation was based on any one of the following: 1) nasopharyngeal (or endotracheal if intubated) aspirate for COVID-19 nucleic acid reverse transcriptase–polymerase chain reaction (RT-PCR), 2) a positive serum-specific COVID-19 IgM test, or 3) demonstration of seroconversion of serum-specific COVID-19 IgG (negative to positive) or a 4-fold rise in IgG titers.

Data extraction. A centralized, online COVID-19 standardized database was set up using the Research Electronic Data Capture system, with the main coordinating center in Singapore, and was accessible to all site investigators.¹⁴ Data were extracted from medical records and entered by trained staff at each participating site. Data extracted included epidemiological, clinical, laboratory, and outcome data. Baseline data were captured on presentation to the hospital. Outcome data were captured on discharge from the hospital and refer to the highest severity of illness or level of support throughout the disease course. The centralized registry database was queried on November 26, 2020.

Outcomes. The primary outcome was severity of COVID-19 infection as defined by the WHO: mild, moderate, severe, or critical.¹⁵ Secondary outcomes included the need for any respiratory support (including oxygen), organ dysfunction (defined by the International Pediatric Sepsis Consensus Conference),¹⁶ and hospital mortality.

Statistical analysis. Patients who fulfilled the WHO definition for confirmed COVID-19 infection were treated as binary data and classified into two broad severity categories: mild/moderate and severe/critical. All the variables were summarized in terms of the previously mentioned severity categories. Categorical and continuous variables were presented as counts (percentages) and median (interquartile range), respectively. Associations between severity groups and other categorical variables were evaluated using the χ^2 test, whereas the association between continuous variables were tested using the Kruskal-Wallis test. In addition to laboratory investigations, which were not routine at all sites, missing data were minimal ($< 10\%$) for all variables. No imputation for missing data was done. Univariate and multivariable logistic regression models were used to identify risk factors for severe/critical disease. To account for correlated patient responses within countries, models were analyzed with PROC GENMOD with binomial distributions and logit link functions. Quantitative associations from GEMOD analysis were expressed as odds ratios with a 95% CI. Modeling was performed using a manual backward elimination

method with an exclusion criterion set at $P > 0.1$. Adjustment for country was fixed in the multivariable model. All tests were two tailed, and statistical significance was set as $P < 0.05$. SAS/ACCESS[®] v. 9.4 (SAS Institute Inc., Cary, NC) was used for the analysis.

RESULTS

Eight hospitals across seven countries (China, Japan, Singapore, Malaysia [two hospitals], Indonesia, India, and Pakistan) contributed data to this study. A total of 849 children suspected of having COVID-19 infection were enrolled between January 28, 2020 and November 6, 2020, of which 260 (30.6%) were laboratory-confirmed COVID-19 cases. Approximately half the cases were from Singapore (130 of 260, 50%). Laboratory confirmation was obtained via RT-PCR in 249 of 260 (95.8%) cases, IgM in 2 of 260 (0.8%) cases, and IgG seroconversion in 48 of 260 (18.5%) cases. The median (interquartile range) age of COVID-19 cases in the database was 6.5 (2.0, 12.0) years (Table 1). The median (interquartile range) age of COVID-19 cases was lowest in India [3.0 (1.0, 8.0) years] and highest in Indonesia [12.5 (11.0, 14.5) years]. There were slightly more male cases (about 50–60%) in most participating countries, except for Indonesia and Japan (25% and 33%, respectively). In all countries, the most commonly reported contact history with COVID-19 cases was in household settings.

Records of clinical symptoms were available for 256 of 260 (98.5%) patients. At presentation, a significant proportion (102 of 256, 39.8%) of COVID-19 cases was asymptomatic (Table 2). The majority of these asymptomatic cases was identified through contact tracing and testing, as well as screening practices (e.g., screening for pre-operative patients). Fever was the most common (98 of 154, (63.6%) symptom, followed by cough (60 of 154, 39.0%) and coryza (36 of 154, 23.4%). Lower respiratory signs at presentation were present in only 2 of 256 ($< 1\%$) COVID-19 cases. Severe/critical cases were more likely to have fever, cough, poor feeding, diarrhea, vomiting, and seizures at presentation, compared with mild/moderate cases (Table 2). Laboratory investigations for patients were not routine in most centers' patients (Table 3). Among cases with available laboratory investigations data, a lower hemoglobin level [9.5 g/dL [8.6, 11.4 g/dL] versus 13 g/dL [12.4, 13.8 g/dL]; $P < 0.001$], neutrophil count (2.9 neutrophils $\times 10^9/L$ [2.1, 4.2 neutrophils $\times 10^9/L$] versus 5.2 neutrophils $\times 10^9/L$ [3.5, 8.3 neutrophils $\times 10^9/L$]; $P < 0.001$), and albumin level (3.4 g/dL [2.4, 4.1 g/dL] versus 4.1 g/dL [3.9, 4.4 g/dL]; $P = 0.002$); and a higher alanine aminotransferase level [35.9 (20.0, 56.0) U/L versus 16.5 (13.0, 22.0) U/L; $P = 0.002$] and C-reactive protein level [116.0 (0.5, 179.1) mg/L versus 1.6 (0.2, 5.0) mg/L; $P = 0.034$] were associated with severe/critical disease compared with mild/moderate disease. Viral and bacterial co-infection were identified in only nine and seven cases, respectively.

Outcome reporting was complete in 256 of 260 (98.5%) patients. Severe/critical COVID-19 infection was reported in 26 of 256 (10.2%) patients (Table 4). Infants (< 12 months) were more likely to develop severe/critical COVID-19 compared with older children (8 of 26 [30.8%] versus 18 of 230 [7.8%]; $P = 0.002$). The presence of a comorbidity was

TABLE 1
Country-specific demographic characteristics of coronavirus disease 2019 cases and severity outcome in Asia

Demographics	Country								Severity			P value*
	China (n = 30)	Indonesia (n = 8)	India (n = 33)	Japan (n = 21)	Malaysia (n = 19)	Pakistan (n = 19)	Singapore (n = 130)	Mild/moderate (n = 230)	Severe/critical (n = 26)			
Age, y	10 (5-13)	12.5 (11-14.5)	3 (1-8)	4 (2-9)	6 (2-14)	4 (1-11)	7 (3-12)	7 (3-12)	4 (1-12)	0.204		
Weight, kg	26.1 (10.0-26.1)	34.0 (24.0-39.5)	11.0 (7.5-24.0)	15.0 (12.0-17.0)	14.6 (10.6-25.0)	15.0 (9.0-35.0)	23.3 (12.9-44.8)	20.5 (12.0-36.5)	12.5 (6.5-36.0)	0.039		
Male	17 (56.7)	2 (25.0)	17 (51.5)	7 (33.3)	10 (52.6)	17 (89.5)	73 (56.2)	123 (53.5)	18 (69.2)	0.148		
Infants	2 (6.7)	0 (0.0)	10 (30.3)	2 (9.5)	2 (10.5)	4 (21.1)	8 (6.2)	18 (7.8)	8 (30.8)	0.002		
Breastfeeding	0 (0.0)	0 (0.0)	7 (77.8)	1 (100)	2 (100)	2 (100)	3 (37.5)	10 (62.5)	5 (83.3)	0.616		
Travel history	11 (36.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	1 (5.3)	77 (59.2)	88 (38.6)	2 (14.3)	0.088		
Exposure to confirmed case	27 (90.0)	5 (62.5)	24 (72.7)	20 (95.2)	16 (84.2)	0 (0.0)	115 (88.5)	200 (90.5)	5 (45.5)	< 0.001		
Health care	1 (3.3)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.1)	5 (2.2)	1 (3.8)	0.478		
School	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (0.8)	2 (0.9)	0 (0.0)	1.000		
Household	23 (76.7)	4 (50.0)	24 (72.7)	12 (57.1)	13 (68.4)	0 (0.0)	113 (86.9)	183 (79.6)	4 (15.4)	< 0.001		
Other	2 (6.7)	0 (0.0)	0 (0.0)	8 (38.1)	2 (10.5)	0 (0.0)	2 (1.5)	14 (6.1)	0 (0.0)	0.373		
Comorbidities	1 (3.3)	3 (37.5)	7 (21.2)	2 (9.5)	4 (21.1)	17 (89.5)	17 (13.1)	29 (12.6)	20 (76.9)	< 0.001		
Cardiovascular	0 (0.0)	0 (0.0)	2 (6.1)	0 (0.0)	2 (10.5)	4 (21.1)	0 (0.0)	3 (1.3)	4 (15.4)			
Gastrointestinal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (15.8)	0 (0.0)	1 (0.4)	2 (7.7)			
Hematology/oncology	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (5.3)	4 (21.1)	0 (0.0)	1 (0.4)	5 (19.2)			
Neurological	0 (0.0)	0 (0.0)	3 (9.1)	2 (9.5)	0 (0.0)	2 (10.5)	2 (1.5)	5 (2.2)	4 (15.4)			
Renal	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (0.4)	1 (3.8)			
Respiratory	0 (0.0)	2 (25.0)	1 (3.0)	0 (0.0)	1 (5.3)	1 (5.3)	1 (0.8)	2 (0.9)	3 (11.5)			
Other	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	14 (10.8)	16 (7.0)	1 (3.8)			

Categorical variables are presented as count (percentage) and continuous variables are presented as median (interquartile range).
* The P value shows the differences between the two severity groups.

TABLE 2
Clinical presentation of coronavirus disease 2019 cases and severity outcome in Asia

Clinical symptoms	Country						Severity		P value*	
	China (n = 30)	Indonesia (n = 8)	India (n = 33)	Japan (n = 21)	Malaysia (n = 19)	Pakistan (n = 19)	Singapore (n = 130)	Mild/moderate (n = 230)		Severe/critical (n = 26)
Asymptomatic	7 (30.4)	1 (25.0)	16 (57.1)	6 (37.5)	7 (36.8)	0 (0.0)	67 (58.8)	102 (52.6)	0 (0.0)	0.002
Fever	10 (33.3)	6 (75.0)	11 (33.3)	13 (61.9)	10 (52.6)	13 (68.4)	36 (27.7)	78 (33.9)	20 (76.9)	< 0.001
Cough	15 (50.0)	7 (87.5)	6 (18.2)	3 (14.3)	4 (21.1)	5 (26.3)	20 (15.4)	49 (21.3)	11 (42.3)	0.017
Coryza	4 (13.3)	1 (12.5)	1 (3.0)	3 (14.3)	2 (10.5)	0 (0.0)	26 (20.0)	36 (15.7)	1 (3.8)	0.105
Sore throat	1 (3.3)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (10.0)	15 (6.5)	0 (0.0)	0.180
Wheezing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Crepitations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	0 (0.0)	0 (0.0)	1 (3.8)	0.367
Headache	1 (3.3)	1 (12.5)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.1)	7 (3.0)	0 (0.0)	0.633
Irritability	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)	2 (0.9)	0 (0.0)	0.008
Refuse feeding	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (5.3)	0 (0.0)	2 (0.9)	2 (7.7)	0.001
Diarrhea	1 (3.3)	1 (12.5)	3 (9.1)	2 (9.5)	2 (10.5)	5 (26.3)	6 (4.6)	13 (5.7)	6 (23.1)	< 0.001
Vomiting	0 (0.0)	0 (0.0)	3 (9.1)	3 (14.3)	0 (0.0)	5 (26.3)	3 (2.3)	5 (2.2)	9 (34.6)	0.001
Seizures	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	2 (10.5)	0 (0.0)	1 (0.4)	2 (7.7)	< 0.001

NA = not applicable. Categorical variables are presented as count (percentage).

* The P value shows the differences between the two severity groups.

also associated with severe/critical disease compared with no comorbidity (20 of 26 [76.9%] versus 29 of 230 [12.6%]; $P < 0.001$).

Pulmonary organ dysfunction occurred in 12 patients, six of whom required invasive respiratory support, and five fulfilled criteria for pediatric acute respiratory distress syndrome (Table 4). Non-invasive respiratory support, including oxygen, was required in five patients. Organ dysfunctions were also seen in other systems (Table 4). The overall mortality was 6 of 256 (2.3%) cases, all of which occurred in Pakistan ($n = 5$) and India ($n = 1$). There were no cases of MIS-C in this cohort. In the multivariable logistic regression, infant age group (adjusted odds ratio [aOR], 4.65; 95% CI, 1.90–11.38), presence of comorbidities (aOR, 8.08; 95% CI, 1.79–36.41), and cough on presentation (aOR, 2.41; 95% CI, 1.32–4.39) were associated with severe/critical COVID-19 infection (Table 5).

DISCUSSION

This epidemiological study of pediatric COVID-19 infections found that the common presenting clinical signs and symptoms of COVID-19 in children in our Asian hospital network were similar: fever, cough, and coryza. The overall asymptomatic rate was about 40%. With the exception of Pakistan, which only included cases admitted to the ICU, children with COVID-19 also had similar minimal abnormalities in laboratory parameters at presentation. Pediatric exposure to SARS-CoV-2 was reported to occur mainly in household settings. The rate of severe/critical COVID-19 disease was 0.8% to 5.3% in Singapore, Malaysia, Japan, and China compared with 16% in India, 37.5% in Indonesia, and 78% in Pakistan. The higher rates in India, Indonesia, and Pakistan were possibly a manifestation of testing and hospitalization prioritization for children with more severe clinical manifestation. No children with confirmed COVID-19 met the MIS-C criteria in our registry. Overall mortality was 2.3% (6 of 256) in our registry, with all deaths reported from India and Pakistan. Infant age group (< 12 months), the presence of comorbidities, and cough on presentation were identified as risk factors associated with severe/critical COVID-19 infection in children.

In our regional registry, pediatric COVID-19 symptoms on presentation were mostly consistent with an upper respiratory tract infection, with fever, cough, and coryza being the most common symptoms. Transmission was mostly reported to occur in household settings. As some countries may have enforced nation-wide lock downs or school closures, the risk of SARS-CoV-2 transmission in the school setting was not apparent during this study period. However, published studies have reported the low risk of SARS-CoV-2 transmission in educational settings as well as differences in infection rates within households by age group.^{17–19} The prevalence of gastrointestinal symptoms including diarrhea, vomiting, and poor feeding, which have been associated with MIS-C, were also associated with severe/critical infection.²⁰ Raised C-reactive protein values in COVID-19 cases were only evident in Pakistan, which is not surprising because all cases were admitted to the ICU. Evidence of significant systemic inflammatory response during the infection is known to be associated with severe disease in adults. None of the cases in our registry fulfilled the criteria for MIS-C. However, our study was not designed specifically to investigate MIS-C, which can occur weeks after SARS-CoV-2 infection, and RT-PCR/IgM may no longer be positive.⁵

The epidemiologic profiles of cases among each represented country were different. In Singapore, we observe that the majority of cases were associated with travel (59%) and being exposed to a positive household close contact (87%). In Malaysia, however, the nationwide movement restriction order likely accounted for the lower proportion of travel-associated cases (10.5%).^{21–23} In contrast, in Pakistan, despite publishing mitigation guidelines (*National Action Plan for Corona Virus Disease [COVID-19] Pakistan*²⁴), transmission in the form of local community spread of mostly asymptomatic cases was observed.²⁵ The presence of comorbidities was also greater in countries such as Pakistan (90%) and Indonesia (38%), compared with China (3%), Japan (10%), Singapore (13%), and Malaysia (21%). It is not entirely clear from this registry study why these centers had a greater proportion of patients with comorbidities, although we suspect it could be a result of admission prioritization for children with a more severe clinical manifestation in the group with comorbidities, or an exacerbation or increased need for medical care resulting from the underlying comorbid condition itself during the pandemic.

TABLE 3
Laboratory parameters of coronavirus disease 2019 cases and severity outcome in Asia

Laboratory parameters	Country								Severity			P value*
	China (n = 30)	Indonesia (n = 8)	India (n = 33)	Japan (n = 21)	Malaysia (n = 19)	Pakistan (n = 19)	Singapore (n = 130)	Mild/moderate (n = 230)	Severe/critical (n = 26)			
Hemoglobin, g/dL	13.1 (11.5–14.2)	13.0 (10.1–13.6)	10.8 (10.2–11.9)	12.8 (12.5–12.9)	12.8 (11.3–15.5)	9.3 (8.2, 11.4)	13.1 (12.4, 13.9)	13 (12.4, 13.8)	9.5 (8.6, 11.4)	< 0.001		
WBC, ×10 ⁹ cells/L	6.2 (5.0–8.2)	8.4 (4.9–14.6)	11.8 (5.4–23.3)	5.9 (5–10.8)	9.5 (8.6, 11.5)	10.3 (6.3, 15.6)	7.8 (6.4, 9.8)	7.6 (6.0, 10.0)	9.8 (6.3, 18.9)	0.053		
Lymphocyte, ×10 ⁹ /L	2.7 (2.0–3.5)	3.0 (2.5–3.9)	4.9 (4.8–5.1)	2.9 (2.5–7.6)	4.0 (2.7–5.2)	2.7 (1.3–5.7)	3.3 (2.5–5.25)	3.2 (2.5–4.7)	4.3 (1.6–5.7)	0.744		
Neutrophil, ×10 ⁹ /L	2.1 (2.0–2.6)	4.8 (3.8–9.9)	15.0 (1.6–15.2)	2.2 (1.7–2.2)	4.3 (1.6–6.8)	5.7 (4.6–10.6)	3.0 (2.2–4.1)	2.9 (2.1–4.2)	5.2 (3.5–8.3)	< 0.001		
Platelets, ×10 ⁹ /L	257 (227–298)	336 (290–412)	139 (117–347)	254 (198–300)	278 (196–345)	233 (103–338)	334 (282–380)	318 (247–372)	295 (103–394)	0.249		
APTT, s	26 (22.7–34.3)	34.7 (32.4–37.4)	32 (29.5–39.6)	35 (33.8–36.7)	29.6 (29.6–29.6)	28.8 (26.6–36.7)	41.8 (41.8–41.8)	33.5 (28.8–36.7)	29.7 (26.9–40.4)	0.700		
PT, s	11.1 (10.8–11.6)	14 (13–14.5)	15 (14.4–15.5)	Not reported	10.6 (10.6–10.6)	13.2 (12.6–14.7)	13.5 (13.5–13.5)	13.3 (11.6–14.4)	13 (12.6–17.6)	0.457		
INR	0.96 (0.93–1)	1 (0.915–1.11)	1.04 (0.97–1.2)	1.02 (1.02–1.04)	0.98 (0.98–0.98)	1.3 (1.2–1.4)	1.09 (1.09–1.09)	1.0 (1.0–1.1)	1.2 (1.2–1.7)	0.004		
Total protein, g/dL	8.6 (6–8.7)	Not reported	6.1 (4.4–6.5)	6.9 (6.8–6.9)	7.6 (7.6–7.6)	Not reported	7.4 (7–7.8)	7.4 (7.0–7.8)	6.9 (5.7–7.2)	0.168		
Albumin, g/dL	4.8 (4.5–5.2)	Not reported	3.8 (2.6–4.4)	4.4 (4.4–4.6)	3.9 (3.9–4.2)	3.2 (2.4–3.4)	4.1 (3.9–4.4)	4.1 (3.9–4.4)	3.4 (2.4–4.1)	0.002		
Bilirubin, μmol/L	10.8 (5.3–13.7)	Not reported	0.6 (0.3–0.8)	0.4 (0.4–0.5)	4.7 (3.7–6.5)	6.8 (1.91–11.1)	6 (5–6)	6 (4–8)	9.1 (3.4–12.0)	0.406		
AST, U/L	47 (22–48)	24 (19–28)	26.35 (21–35)	43 (39–43)	38 (22–59)	37.5 (28–122)	27 (21–35)	27 (21–37)	32 (21–39)	0.665		
ALT, U/L	38 (33–55)	31 (25–44)	17.2 (9–50)	19 (17–20)	25 (16.5–41)	41 (23.5–61)	16 (13–21)	16.5 (13–22)	35.9 (20–56)	0.002		
Urea, mmol/L	5.1 (1.3–8.3)	1.15 (1.1–1.2)	1.4 (0.8–1.6)	1.6 (0.8–5.1)	5.3 (5.1–6.6)	0.0 (3.6–8.9)	3.45 (2.7–4.1)	3.4 (1.4–5.1)	4.0 (1.1–8.9)	0.708		
Sodium, mmol/L	137 (135–138)	145 (141–145)	141 (139–143)	138 (137–138)	140 (138–140)	136 (132–140)	141 (140–142)	139 (137–142)	138.7 (133–143)	0.950		
Potassium, mmol/L	5.72 (5.6–5.9)	4.6 (4.4–5.1)	4.0 (3.2–4.5)	4.3 (4–4.4)	3.7 (3.7–3.9)	3.6 (3.3–3.8)	4.3 (4–4.7)	4.3 (3.8–4.6)	3.7 (3.3–3.9)	0.006		
Creatinine, μmol/L	39.5 (23.4–50.1)	48 (48–49.5)	33 (22–40.5)	21 (21–25)	42.9 (35–44.1)	44.1 (35.4–106)	28 (20–47)	35 (26.52 to 48)	37.4 (26–106)	0.463		
CRP, mg/L	1.0 (0.1–4.5)	5.0 (5.0–5.0)	0.4 (0.2–20.9)	3.2 (1.8–4.1)	0.2 (0.2–0.3)	179.1 (163.3–192.0)	1.2 (1.0–2.3)	1.6 (0.2–5.0)	116.0 (0.5–179.1)	0.034		

ALT = alanine transaminase; APTT = activated thromboplastin time; AST = aspartate transaminase; CRP = C-reactive protein; INR = international normalized ratio; PT = prothrombin time; WBC = white blood cell count. Continuous variables are presented as median (interquartile range).

* The P value shows the differences between the two severity groups.

TABLE 4
Outcomes of coronavirus disease 2019 cases in Asia

Outcomes	Country										Severity		P value*	
	China (n = 30)	Indonesia (n = 8)	India (n = 33)	Japan (n = 21)	Malaysia (n = 19)	Pakistan (n = 19)	Singapore (n = 130)	Mild/moderate (n = 230)	Severe/critical (n = 26)					
Severity														
Mild	29 (96.7)	5 (62.5)	24 (77.4)	20 (95.2)	18 (94.7)	4 (22.2)	128 (99.2)	4 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Moderate	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Severe	1 (3.3)	3 (37.5)	3 (9.7)	1 (4.8)	1 (5.3)	12 (66.7)	1 (0.8)	12 (66.7)	1 (5.3)	1 (5.9)	1 (0.8)	1 (0.8)	1 (0.8)	< 0.001
Critical	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.005
Oxygen therapy	1 (20.0)	3 (37.5)	3 (9.4)	1 (4.8)	0 (0.0)	10 (55.6)	1 (0.8)	10 (55.6)	1 (5.9)	1 (5.9)	1 (0.8)	1 (0.8)	1 (0.8)	0.077
HFNC	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	3 (16.7)	0 (0.0)	3 (16.7)	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.007
CPAP	0 (0.0)	0 (0.0)	1 (3.1)	1 (4.8)	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
BIPAP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Mechanical ventilation	0 (0.0)	0 (0.0)	3 (9.4)	0 (0.0)	0 (0.0)	3 (16.7)	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Organ dysfunction														
Cardiovascular	1 (3.3)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
Pulmonary	0 (0.0)	2 (25.0)	1 (3.1)	0 (0.0)	0 (0.0)	9 (50.0)	0 (0.0)	9 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
Neurological	0 (0.0)	0 (0.0)	3 (9.4)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.007
Hepatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	2 (1.6)	1 (5.6)	0 (0.0)	0 (0.0)	2 (1.6)	2 (0.9)	1 (4.0)	0.267
Renal	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	4 (22.2)	0 (0.0)	4 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	4 (16.0)	0.000
Hematological	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	5 (27.8)	0 (0.0)	5 (27.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	4 (16.0)	0.001
Hospital duration, d	13 (9, 17)	8 (7, 17)	15 (11, 19)	6.5 (5.9)	9 (8, 12)	7 (4, 13)	11 (8, 20)	11 (8, 20)	11 (8, 19)	11 (8, 19)	11 (8, 20)	11 (8, 19)	8 (6, 12)	0.014
Highest inpatient status														
General ward	3 (60.0)	7 (87.5)	26 (78.8)	10 (90.9)	17 (100)	0 (0.0)	130 (100)	0 (0.0)	188 (97.4)	4 (16.0)	4 (16.0)	188 (97.4)	4 (16.0)	< 0.001
Intermediate care	1 (20.0)	0 (0.0)	3 (9.1)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	3 (12.0)	3 (12.0)	1 (0.5)	3 (12.0)	
ICU	1 (20.0)	1 (12.5)	4 (12.1)	0 (0.0)	0 (0.0)	18 (100)	0 (0.0)	18 (100)	4 (2.1)	18 (72.0)	18 (72.0)	4 (2.1)	18 (72.0)	
Mortality	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	5 (27.8)	0 (0.0)	5 (27.8)	0 (0.0)	6 (25.0)	6 (25.0)	0 (0.0)	6 (25.0)	< 0.001

BIPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; HFNC = high-flow nasal cannula; ICU = intensive care unit. Categorical variables are presented as count (percentage) and continuous variables are presented as median (interquartile range).

* The P value shows the differences between the two severity groups.

TABLE 5
Multivariable analysis of predictive factors for severe/critical coronavirus disease 2019 in Asian children

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Infant	2.38	1.26–4.88	0.008	4.65	1.90–11.38	< 0.001
Comorbidities	3.82	1.03–14.18	0.045	8.08	1.79–36.41	0.007
Cough	1.60	1.14–2.24	0.006	2.41	1.32–4.39	0.004

OR = odds ratio; CI = confidence interval.

Health-care systems and public health pandemic response to COVID-19 in Asia are highly variable. In Singapore, contact tracing and diagnostic testing are widespread, and all confirmed COVID-19 cases were isolated institutionally until they were deemed non-infective before patients were discharged from the hospital, leading to a prolonged duration of hospital stay median (interquartile range) of 11 (8, 20) days, despite the majority of cases being asymptomatic (67 of 130, 59%).^{26,27} Similarly, many of the patients in Japan and Malaysia were asymptomatic, and only one case each required continuous positive airway pressure or high-flow nasal cannula, respectively. In Malaysia, patients were kept in the hospital until 14 days after the onset of symptoms. In Japan and Malaysia, the median (interquartile range) hospital stay was 6.5 (5.0, 9.0) and 9 (8.0, 12.0) days, respectively. In contrast, the recruiting center in Pakistan, which was situated in Karachi, the largest urban city of Pakistan, had the highest case density in the country. This unit received referrals of patients with underlying acute and chronic diseases from other hospitals, many of whom were found to test positive for COVID-19 infection. Cases referred here were unlike the asymptomatic cases identified from contact tracing (these were advised to quarantine at home). On the contrary, patients seen here had significant symptoms warranting admission to the pediatric ICU. A high proportion of these patients developed organ dysfunction (82%) and required respiratory support (78%). Mortality in this unit was 26%.

Although differences in testing capacity, health systems, and pandemic response strategies across Asia are potential reasons for the differences described, differences in COVID-19 infection rates and outcomes could also be present as a result of genetic factors, cultural practices, environmental exposures, or combinations of biological and social factors. For example, angiotensin converting enzyme-2 receptor polymorphisms exist across gender and races, and have been implicated in affecting the severity of COVID infection in different regions.²⁸ The results of our study indicate that, even within the “Asian” racial group, these differences may exist, and in-depth studies to disentangle the role of each contributing factor is vital. India⁸ and Pakistan⁹ have previously reported cases of MIS-C, whereas none of the severe/critical cases in our registry from Singapore, Malaysia, Indonesia, Japan, and China met the criteria for MIS-C. Our study also suggests that extrapolation of data from other geographic or racial populations may be inappropriate, and further investigations should include Asian representation.

This study leverages on a multi-center research network to include data from seven countries across Asia. All included sites are national COVID-19 referral centers. Nevertheless, the number of sites included were few and may not be fully representative of all cases in each country. Individual

centers/countries have unique health-care policies in managing this pandemic, and criteria for screening suspected cases, indications for hospital admission, duration of stay, need for laboratory testing, and so on may differ and bias our results. Representation from northern regions of south-east Asia including Thailand, Laos, Cambodia, and Myanmar, which have unique cultures, demographics, and health-care profiles, are missing. Sites were encouraged to enter consecutive patient's data on a weekly basis to ensure up-to-date reporting; however, as this was not monitored and mandated, it may have resulted in non-consecutive enrollments or missing data. The inclusion of only ICU-level patients from Pakistan may have biased the results. Bias may have also been introduced because this study used passive surveillance methods that were reliant on reporting by the respective hospitals. The possibility of false-positive/false-negative COVID-19 PCR, IgM, or IgG results cannot be excluded, although the majority of our cases were confirmed via PCR, which is known to have high sensitivity and specificity. Last, after discharge from the hospital, this study did not include any further follow-up visits. Therefore, intermediate to long-term complications were not captured.

CONCLUSION

The clinical presentation and basic laboratory parameters of SARS-CoV-2 infection in children from seven Asian countries were similar. The overall asymptomatic rate was about 40%, and mortality was 2.3%, with all deaths reported from Pakistan and India. No cases of MIS-C were identified in our study. Risk factors for severe/critical pediatric COVID-19 infection were found to be age < 12 months, cough at presentation, and presence of comorbidities. Further data will be accrued in the PACCOVRA registry to determine the impact of pediatric COVID-19 over time and over larger geographic regions in Asia.

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