Clinical and Laboratory Profile, Management and Outcome of Pediatric SARS-CoV-2 Infection Admitted at the Philippine General Hospital

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ABSTRACT

Background. The Philippines has recorded over 470,000 COVID-19 cases in children, with over 1,500 deaths during the same period. Although a Philippine online pediatric COVID-19 registry exists, this only relies on passive surveillance.

Objectives. This study determined the clinical and laboratory profile, risk factors for severe COVID-19, and mortality, management, and outcome of pediatric SARS-CoV-2 patients admitted at the Philippine General Hospital (PGH) from April 2020 to June 2022 to fill in knowledge gaps on the epidemiology of COVID-19 infection in children.

Methods. This was a retrospective cohort study of pediatric COVID-19 cases admitted at the PGH, a designated COVID referral center during the study period. Demographic and clinical profile, risk factors, comorbidities, laboratory and radiologic findings, management, and outcomes across different disease severity states were gathered by chart review and the data were analyzed using STATA 17.

Results. There were 448 pediatric patients admitted and diagnosed with COVID-19 during the study period. Most patients belonged to the 1-5-year age group (25.9%), had no known exposure to a COVID-19 case (65.4%), were mild cases (37.3%%), and did not receive any dose of the COVID-19 vaccine (96.7%). The most common presenting symptoms across all disease categories were fever (44.4%), cough (28.6%), and shortness of breath (26.6%). Multisystem inflammatory syndrome in children (MIS-C) presented with fever (100%) and rash (53.9%). The risk factors for severe disease were the presence of a congenital anomaly lung disease, and elevated procalcitonin. Most patients with MIS-C were previously well with no comorbidities. Laboratory findings which were markedly elevated among severe and critical cases were ESR, CRP, D-dimer, LDH, and IL-6. Ferritin, procalcitonin (PCT) and IL-6 were elevated only in severe to critical COVID-19 cases and remained within normal for the other disease categories. As to treatment, asymptomatic, mild, and moderate cases were given supportive medications (zinc, vitamin D, and vitamin C), while investigational drugs particularly corticosteroids, IVIG, and remdesivir, were used in severe cases. Antibiotics were given to 71.7% of patients at the outset. As to the outcomes, 89% recovered, while 8.9% died. The case fatality rate from COVID-19 infection was at 2.2%.

Conclusion. Admitted pediatric COVID-19 cases are generally mild but admission is due to underlying illness or comorbidities. Those with severe to critical cases have underlying comorbidities and had either progression or complications due to COVID disease. D-dimer, LDH, IL-6, ferritin and procalcitonin were elevated among severe and critical cases which can be utilized as inflammatory markers.

Keywords: COVID-19, SARS-CoV-2, clinical profile, pediatric patients

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INTRODUCTION

Since the emergence of coronavirus disease 2019 (COVID-19) in Wuhan, China, last December 2019, there have been 754 million confirmed cases, including 6.8 M deaths, reported to the World Health Organization (WHO) global data as of February 2023.[1] The impact of COVID-19 infection on the pediatric population continues to raise several questions and concerns. Disease burden in children has been monitored and reported by the WHO through various health protection agencies worldwide (e.g., Centers for Disease Control and Prevention, Pan American Health Organization, and locally the Philippine Department of Health). However, diverse facets of the disease are still to be recognized and understood.[2,3]

In the Philippines, as of February 20, 2023, the Department of Health has recorded over 4M confirmed COVID-19 cases, with 66,030 recorded deaths. A total of 477,606 COVID-19 cases have been recorded in children 19 years and below from March 2020 to February 2023. Majority were in children 15 to 19 years old (35.78%), followed by the 10-14 years age group at 24.31%, 0 to 4 years age group at 20.57%, and the 5 to 9 years age group at 19.35%. The incidence of infection in children remained low and comprised about 11.80% of total cases in the Philippines.[4] Majority of infections are mild compared to adults and the most common symptoms are fever, cough, vomiting, diarrhea, sore throat, and dyspnea.[5] The burden of disease was highest among pediatric patients with comorbidities and in those who are immunocompromised. Mortality during the same time period showed that as of February 20, 2023, 1,505 deaths were recorded in children, with a case fatality rate of 0.32%. Among these deaths, most were seen in the 0 to 4 years age group followed by the 15 to 19 years age group, 10-14 years age group, and 5 to 9 years age group.

Children at risk of mortality and severe COVID-19 were identified and found among those at extremes of ages and in those with cardiac disease, pulmonary disease, and obesity. Severe cases were also found among those with elevated serum C-reactive protein, D-dimer, and in those who develop Multisystem Inflammatory Syndrome in Children (MIS-C).[6,7]

Although mortality was highest among children less than 5 years old, age-segregated data on disease severity, hospitalization rates, and risk factors are needed and information on clinical and laboratory profile, management and outcomes, and risk factors of hospitalized COVID-19 cases is important to continue to guide clinicians and policymakers. Locally published reports of COVID-19 cases in the pediatric population are limited. An online pediatric registry for surveillance and analysis of COVID-19 in children nationwide (SALVACION Registry) exists through the initiative of the Pediatric Infectious Disease Society of the Philippines (PIDSP).[8] The registry has been collecting data since July 2020. It relies on passive surveillance and voluntary reporting by healthcare professionals, and has its limitations. To further characterize COVID-19 among hospitalized pediatric patients, this study determined the clinical and laboratory profile, risk factors, managemen,t and outcome of pediatric SARS-CoV-2 infection admitted at the Philippine General Hospital (PGH) from April 2020 to June 2022.

METHODS

Study Design

This was a retrospective cohort study of children with probable and confirmed SARS-CoV-2 infection. All hospitalized pediatric patients below 19 years of age with probable and confirmed COVID-19 infection and admitted during the study period were included, as well as hospitalized cases who fulfilled the WHO criteria for Multisystem Inflammatory Syndrome in Children (MIS-C).

Pediatric patients were initially screened for the presence of COVID-19 by assessing for exposure, clinical evaluation, review of laboratory tests, and chest imaging. If any of the above is suggestive of COVID-19, the diagnosis was confirmed through RT-PCR. Appropriate specimens were submitted, such as samples collected from the upper (pharyngeal swabs, nasal swabs, nasopharyngeal secretions) and/or lower airways (sputum, airway secretions, bronchoalveolar lavage fluid). Cases were diagnosed and classified in accordance with existing guidelines set out by the Pediatric Infectious Disease Society of the Philippines available at the time of patient's admission.[9–13]

Confirmed COVID-19 patients were patients with laboratory-confirmed PCR result done at a national reference laboratory, a subnational reference laboratory, and/or DOH-certified laboratory testing facility. Probable COVID-19 cases were patients who met one of the following criteria:

a. Met the clinical criteria AND is a contact of a probable or confirmed case, or linked to a COVID-19 cluster
b. A suspect case with chest imaging showing findings suggestive of COVID-19 disease
c. A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause
d. Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or linked to a COVID-19 cluster.

The COVID-19 classification can be found in the Appendix.[10]

Data Collection

Chart review was done and demographic information, exposure history, COVID-19 vaccination status, comorbidities, clinical manifestations, laboratory findings, radiologic and imaging results of patients admitted at the COVID-19 ward of the pediatric unit of the hospital were recorded from admission to discharge or death. If repeated diagnostic tests

were performed, all test results were recorded. Management and interventions related to COVID-19 were documented. Final outcome was determined on the last hospital day and listed as any of the following: death, discharged improved, worsening of symptoms or transferred to another hospital. All patient information and data extracted from medical records of patients were noted using a case report form (CRF). The study did not interfere with patient management during the entire period of hospitalization.

The study was approved by the University of the Philippines Manila Research Ethics Board (REB), and adhered to the ethical considerations and principles set out in relevant guidelines, including the Data Privacy Act of 2012, Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethical Guidelines for Health and Health-Related Research (NEGHHR). Each case was given a code and no identifiers were recorded in the case report forms and in the manuscript.

Statistical Analysis

Descriptive statistics (frequencies and percentages) were used for categorical variables, while measures of central tendency (mean, median) and variance (range and standard deviation) were used for continuous variables. Modified Possion regression analysis was used to determine the predictors and risk factors for severity, and cox regression analysis was used for mortality and outcomes. A p-value of <0.05 was considered statistically significant.

RESULTS

There were 448 pediatric COVID-19 cases admitted from April 1, 2020 to June 30, 2022. Four hundred five (90%) were confirmed by RT-PCR while 30 (7.1%) were labeled as probable COVID-19 cases. There were 13 (2.9%) who fulfilled the criteria for MIS-C.

Most were in the 1-5 year-age group (25.9%), followed by the 11-15-year age group (23.2%) and those <1 year old (20.3%). The median age of patients was 7 years old (SD 6.24). Males comprised 58.7% of cases (Table 1).

Most admissions came from the National Capital Region (54.4%) followed by Region IV-A which includes the provinces of Calamba, Laguna, Batangas, Rizal and Quezon (CALABARZON, 37.2%) (Table 1).

Only 133 (29.7)% of patients claimed they were exposed to a known COVID-19 case, while 293 (65.4%) claimed there was no exposure. Majority of cases did not receive any dose of the COVID-19 vaccine (96.7%). Most patients in this cohort were underweight (43%), with only a small proportion of overweight and obese patients (5%). There was only 1 obese patient who developed critical COVID-19 (Table 2).

As to disease severity, 167 (37.3%) cases were predominantly mild and 93 cases (20.8%) were classified as asymptomatic and admitted for another condition. There were patients who were admitted for surgery, trauma, and burn, with no COVID-19 symptoms in the chief complaint. Majority of these mild and asymptomatic cases were from the 11-19 years age group. Sixty-nine (15.4%) were severe and 41 (9.1%) were critical cases and were predominant in the <1 year age group followed by 1-5-year age group.

About 83% of admitted patients with COVID-19 had comorbidities. These comorbidities were underlying surgical condition (16.0%), neurologic condition (14.5%), cardiac condition (14.0%), malignancy (12.3%), and congenital anomaly (11.2%). Most asymptomatic and mild COVID-19 cases had an underlying surgical or traumatic condition on admission, at 44% and 16.17%, respectively while in those with severe COVID-19, the most common comorbidity was the presence of a cardiac condition, congenital anomaly, and neurologic condition. Among those with critical COVID-19, the most common comorbidity was the presence of a neurologic condition, malignancy, congenital anomaly, cardiac condition, and lung disease (Table 2).

The most common presenting symptoms among hospitalized patients with COVID-19 across different disease categories were fever (44.4%), cough (28.6%), shortness of breath (26.6%), vomiting (18.3%), diarrhea (12.9%), and coryza (12%) (Table 2).

There were 13 cases of MIS-C which were mostly seen in the 1-5-year age group (70%). All cases did not receive any COVID vaccines. Ten cases (76.9%) had no underlying comorbidity, while 2 (15.4%) had a concomitant malignancy (B-Cell acute lymphoblastic leukemia). All patients with MIS-C presented with fever. The other symptoms were rash (53.9%), diarrhea (38.5%), cough (38.5%) and vomiting (30.8%).

A summary of laboratory and imaging findings in children with COVID-19 are seen in Tables 3 and 4. Laboratory findings which were markedly elevated among

Table 1. Demographic Characteristics of Admitted Patients

	Frequency (n=448)	%
Age		
<1	91	20.3
1 - 5	116	25.9
6 - 10	79	17.6
11 - 15	104	23.2
16 - 19	58	13.0
Sex		
Male	263	58.7
Female	185	41.3
Region		
NCR - National Capital Region	244	54.4
Region IV-A - CALABARZON	167	37.2
Region III - Central Luzon	29	6.5
CAR - Cordillera Autonomous Region	2	0.5
Region V - Bicol Region	2	0.5
Region VI - Western Visayas	2	0.5
Region II - Cagayan Valley	1	0.2
Region IX - Zamboanga Peninsula	1	0.2

Table 2. Clinical Characteristics of Admitted Pediatric Patients with COVID-19

	Frequency (n = 448)	%
Exposure History		
No	293	65.4
Yes	133	29.7
Unknown	22	4.9
BMI		
Unknown	159	35.5
Underweight	193	43.1
Normal	73	16.3
Overweight	19	4.3
Obese	4	0.8
Vaccination Status		
None	433	96.7
Incomplete	2	0.5
Complete	8	1.7
1 Booster	0	0.0
Unknown	5	1.1
COVID-19 Classification		
Confirmed	403	90.4
Probable	30	6.7
MISC	13	2.9
COVID-19 Disease Severity		
Asymptomatic	93	20.8
Mild	167	37.3
Moderate	65	14.4
Severe	69	15.4
Critical	41	9.1
MIS-C	13	3.0
Presenting Symptoms		
Fever	199	44.4
Cough	128	28.6
Shortness of breath	119	26.6
Vomiting/Nausea	82	18.3
Diarrhea	58	12.9
Coryza/colds	54	12.1
Seizure/s	19	4.2
Headache	15	3.4
Rash	12	2.7
Sore throat	8	1.8
With Comorbidities or Underlying Conditions	372	83.0
Surgical, Traumatic	72	16.0
Neurologic	65	14.5
Cardiac	63	14.0
Malignancy	55	12.3
Congenital Anomaly	50	11.2
Tuberculosis	39	8.7
Other infection	31	6.9
Lung Disease	24	5.3
Kidney Disease	21	4.7
Hematologic	17	3.8
Metabolic	15	3.3
Auto-immune	10	2.2
Hepatic	5	1.1
Immunodeficiency	4	0.9
Pregnancy	3	0.7
Without Comorbidities or Underlying Conditions	76	17.0

Table 3. Laboratory Findings of Admitted Pediatric Patients with COVID-19

	Frequency (n = 448)	%
Hemoglobin		
<110	146	32.7
110 - 135	186	41.7
>135	114	25.6
Hematocrit		
<0.31	105	23.6
0.31 - 0.40	221	49.7
>0.40	119	26.7
White Blood Cells		
<4.5	40	9.0
4.5-11	170	38.2
>11	235	52.8
Neutrophils		
<0.5	118	26.5
0.5-0.70	131	29.5
>0.70	196	44.0
Lymphocytes		
<0.20	194	43.7
0.2-0.5	185	41.6
>0.5	65	14.6
Platelet Count		
<150	92	20.8
150-450	264	59.7
>450	86	19.5
CRP		
Normal <6	84	30.2
High >6	194	69.8
Procalcitonin		
Normal <0.25	123	37.3
High ≥0.25	207	62.7
Interleukin-6		
Normal 0-50	69	32.7
High >50	142	67.3
ESR		
Normal 0-15	17	20.3
High >15	67	79.7
Ferritin		
Low <17.9	6	3.0
Normal 17.9 - 464	116	56.8
High >464	82	40.2
D-dimer		
Normal 0-0.5	14	6.3
High >0.5	208	93.7
LDH		
Low <120	2	1.1
Normal 120-246	24	12.8
High >246	161	86.1
Fibrinogen		
Low <200	9	8.7
Normal 200-400	43	41.7
High >400	51	49.6

Hemoglobin: g/L; WBC: x 10^9/L; Platelet 10^9/L; CRP: mg/L, Procalcitonin ng/ml; ESR mm/hr, IL-6: pg/ml; Ferritin: ng/ml, Fibrinogen: mg/dl; D-dimer ug/ml; LDH: U/L

Table 4A. Radiographic Findings of Admitted Pediatric Patients with COVID-19 (n = 398)

	Frequency	%
Normal X-ray	159	40.0
Opacities		
Unilateral	51	13.0
Bilateral	167	42.6
Pleural Effusion	37	9.3
Consolidation	27	6.3
Atelectasis	25	5.9
Other findings	3	0.7

Table 4B. Chest Tomography Findings of Admitted Pediatric Patients with COVID-19 (n = 71)

	Frequency	%
Ground glass opacities (GGO)	66	93.0
Bilateral GGO (unspecified)	11	15.5
Bilateral central GGO	5	7.0
Bilateral peripheral GGO	4	5.6
Bilateral peripheral and central GGO	23	32.4
Unilateral GGO (unspecified)	15	21.1
Unilateral peripheral GGO	5	7.0
Unilateral peripheral and central GGO	3	4.2
Consolidation		
Unilateral	15	21.2
Bilateral	24	33.8
Pleural Effusion	19	26.7
Other findings	2	0.3

severe and critical cases were ESR, CRP, D-dimer, LDH, and IL-6. All critical and MIS-C patients had elevated D-dimer. Ferritin, procalcitonin (PCT), and IL-6 were elevated only in severe to critical COVID-19 cases and remained within normal for the other disease categories.

As to imaging findings, initial chest radiographs done in 398 cases were read as normal in 159 (40%) and abnormal in 239 (60%) (Table 4A). Bilateral opacities were the most common finding, particularly in moderate, severe, critical, and MIS-C patients. Most asymptomatic and mild cases presented with normal chest radiographs. Consolidation was more common in severe and critical cases.

Of the 71 patients who had a chest CT scan done, 66 (93%) had findings of ground glass opacities, with bilateral (32.4%) followed by unilateral involvement (21.13%). Other imaging findings were bilateral consolidation (33%) and pleural effusion (26.76%) (Table 4B).

Management, complications, and outcomes of admitted patients are seen in Tables 5, 6, and 7. The investigational drugs given were corticosteroids (35.8%), intravenous immunoglobulin (12.1%), remdesivir (11.9%), tocilizumab (1.4%), and convalescent plasma (1.4%). There were five patients (1.0%) who received enoxaparin as treatment for thrombus formation, while 14 (2.9%) received a prophylactic dose of the drug. Supportive medications used include zinc

Table 5. Management of Admitted Pediatric Patients with COVID-19 (n = 448)

	Frequency	%
Treatment / Adjunct		
Corticosteroids	175	35.8
IVIG	59	12.1
Remdesivir	58	11.9
Convalescent Plasma	7	1.4
Tocilizumab	7	1.4
Enoxaparin Treatment	5	1.0
Enoxaparin Prophylaxis	14	2.9
Antibiotics	350	71.7
Zinc	332	68.0
Vitamin D	292	59.8
Vitamin C	220	45.1
Adverse reactions	2	0.4
Respiratory support		
None	247	50.6
Intubation	93	19.1
Low flow oxygen	50	10.3
Face mask	47	9.6
CPAP/BIPAP/NIPPV	9	1.8
High flow oxygen	2	0.4

CPAP: continuous positive airway pressure; BIPAP: bilevel positive airway pressure; NIPPV: nasal intermittent positive pressure ventilation

Table 6. Complications in Admitted Pediatric Patients with COVID-19 (n = 448)

	Frequency	%
With Complications	136	30.4
Nosocomial Infection	69	15.4
Shock	54	12.0
Renal injury	22	4.9
Increased oxygen requirement	14	3.1
Myocarditis	13	2.9
Hepatic injury	13	2.9
Bleeding	12	2.7
Acute respiratory distress syndrome	11	2.5
Pleural effusion	9	2.0
Seizure	8	1.8
Arrhythmia	4	0.9
Pulmonary embolism	2	0.5
Non-pulmonary thrombus	1	0.2
No Complications	312	69.6

Table 7. Outcomes of Admitted Pediatric Patients with COVID-19 (n = 448)

	Frequency	%
Improved	402	89.8
Expired	40	8.9
Transferred to another hospital	1	0.2

sulfate, Vitamin D and Vitamin C. Asymptomatic, mild, and moderate cases were prescribed vitamins like zinc (73.5%), vitamin D (64.3%), and vitamin C (49.9%) while investigational drugs particularly corticosteroids (85.4%), IVIG (35.4%), and remdesivir (33.6%), were used for management for severe, critical, and MIS-C cases. Antibiotics were given in 350 (71.7%) patients at the outset.

Only two patients experienced adverse events while on treatment. One had anaphylaxis from IVIG while the other developed maculopapular rashes associated with remdesivir. Both cases recovered from these adverse events.

Most patients did not require oxygen supplementation on admission (50.6%) as these were asymptomatic to moderate cases. In contrast, majority of severe (54%) and critical (70%) cases required intubation.

Among the cases, 312 (69.6%) did not have complications during their hospitalization. However, 136 patients developed complications from COVID-19, and the most common was nosocomial infections (15.4%). This was the only complication noted among asymptomatic patients (8.6%). Other complications like shock (12.0%), renal injury (4.9%), myocarditis (2.9%), and hepatic injury (2.9%) were seen in patients with severe and critical COVID-19. Shock developed in 70% of patients with critical COVID-19 and in 26% of patients with severe COVID-19. Nine patients developed myocarditis among those with critical COVID-19 and one patient each for moderate and severe COVID-19 cases. The 11 cases of Acute Respiratory Distress Syndrome (ARDS) were noted only among critical cases. Two patients developed pulmonary embolism and one patient had cranial and common iliac vein thrombus formation identified on high resolution CT-Scan (Table 6).

As to the outcome of admitted patients, 402 cases (89.8%) recovered while 40 (8.9%) died from COVID-19 infection (Table 7). Of those who died, 22 (54%) were critical and 9 (13%) were severe cases. Case fatality rate from COVID was at 2.2%

Regression analysis showed that the development of severe disease was associated with several factors (Table 8). The younger age group was more likely to have severe disease. Infants less than 1 year old and children 1-5 years old had 3.4 times and 2.7 times the rate of severe disease compared to adolescents, respectively. The presence of fever (RR 3.15, CI 2.23 - 4.44), cough (3.19, CI 2.39 - 4.28), shortness of breath (4.79, CI 3.55 - 6.48), diarrhea (RR 1.63, CI 1.15 - 2.32) or colds (RR 1.68, CI 1.18 - 2.39) were also significantly associated with disease severity ($p < 0.05$).

The presence of any comorbidity (RR 0.52, CI 0.38 - 0.71) and surgical or traumatic conditions (RR 0.09, CI 0.02 - 0.34) were protective factors. Patients with an underlying lung disease were 2 times more likely to progress to severe COVID-19 compared to children without these conditions (CI 1.40 - 3.12). Congenital anomaly was also associated with a 1.5 higher risk for developing severe disease (RR 1.06 - 2.26). An elevated procalcitonin was the only significant risk factor, with an RR of 2.35 (CI 1.59 - 3.47) (Table 8)

Shortness of breath on admission, procalcitonin >0.05, and platelet count <150, were risk factors for mortality, with HR 3.42 (CI 1.79 - 6.54), HR 2.30 (CI 1.06 - 5.00), and HR 2.04 (CI 1.04 - 4.00), respectively (Table 9).

DISCUSSION

This retrospective cohort study of 448 admitted patients with probable and confirmed COVID-19 described the epidemiology of pediatric SARS-CoV-2 infection in a tertiary urban referral center from April 2020 to June 2022. Majority of cases were confirmed through reverse transcriptase-polymerase chain reaction (RT-PCR) while a minority were labeled as probable COVID-19 cases as they were the cases during the early months of the pandemic where the PCR test is not yet available in the hospital and not yet validated. MIS-C cases were diagnosed based on the WHO definition.

SARS-CoV-2 infects all age groups and in this study, majority of cases occurred in children less than 5. This finding is similar to that of the large-scale cohort study involving Filipino children with COVID-19 reported to the SALVACION Registry from March 2020 to March 2022, and in the Philippine Department of Health COVID-19 health tracker bulletin.[4,14]

Most admissions came from the National Capital Region followed by Regions IV-A [(Calamba, Laguna, Batangas, Rizal, Quezon (CALABARZON)], all densely populated urban areas in the country. Since the main mode of transmission of COVID-19 is via inhalation of respiratory droplets, although only about 30% of patients had exposure to a known case, spread among people in close contact is likely. Transmission can also occur indoor, in crowded settings, and inadequately ventilated spaces.[15]

Majority of cases in this study claim that they were not exposed to a known COVID-19 case. Evidence has long been established that disease transmission may occur even during the pre-symptomatic phase of COVID-19 illness, where infectiousness begins from 2-3 days before symptom onset. There is also evidence of asymptomatic transmission of COVID-19.[16]

In the Philippines, since the COVID-19 vaccination program for children 12-17 years old was implemented only in October 2021 followed by vaccination in children 5-11 years old in February 2022, the majority of admitted children were not vaccinated against COVID-19. The few patients who completed the primary series in this study were either asymptomatic or mild cases, except for one patient with hydronephrosis who had severe COVID-19. All fully vaccinated patients were sent home improved supporting the role that vaccination plays in protecting children against severe disease and hospitalization.[17,18]

The spectrum of COVID-19 ranged from asymptomatic to critical illness. What is known is that infected children have milder symptoms and are less likely to be hospitalized than adults. The COVID-19 severity classification in pediatric patients was defined based on clinical features, laboratory testing, and chest x-ray imaging, and cases are classified as asymptomatic, mild, moderate, severe, or critical disease.[9]

Most of the patients classified as asymptomatic were admitted for another condition and COVID-19 was detected

Table 8. Crude Associations between Covariates and Disease Severity among Filipino Pediatric Patients Admitted for COVID-19[a]

Characteristic	Total n	Non-severe		Severe/Critical/MIS-C		Crude RR (95% CI)
		n 325	% 72.5	n 123	% 27.5	
Age						
<1	91	49	53.9	42	46.2	3.40 (2.17 – 5.32) **
1 – 5	116	74	63.8	42	36.2	2.67 (1.69 – 4.21) **
6 – 10	79	62	78.5	17	21.5	1.58 (0.89 – 2.81)
11 – 19	162	140	86.4	22	13.6	Ref (1.00)
Sex						
Male	263	191	72.6	72	27.4	Ref (1.00)
Female	185	134	72.4	51	27.6	1.01 (0.74 – 1.37)
Presenting Symptoms						
Fever	199	111	55.8	88	44.2	3.15 (2.23 - 4.44)**
Cough	128	59	46.1	69	53.9	3.19 (2.39 - 4.28)**
Shortness of breath	119	41	34.4	78	65.6	4.79 (3.55 - 6.48)**
Diarrhea	58	34	58.6	24	41.4	1.63 (1.15 - 2.32)*
Coryza/colds	54	31	57.4	23	42.6	1.68 (1.18 - 2.39)*
Vomiting/nausea	82	61	74.4	21	25.6	0.92 (0.61 - 1.38)
Comorbidities						
Any comorbidity	371	283	76.3	88	23.7	0.52 (0.38 - 0.71)**
Surgical/Traumatic	72	70	97.2	2	2.8	0.09 (0.02 - 0.34)**
Lung disease	24	11	60.0	13	54.2	2.09 (1.40 - 3.12)**
Congenital anomaly	50	30	45.8	20	40.0	1.55 (1.06 - 2.26)*
Neurologic	65	46	70.8	19	29.2	1.08 (0.71 - 1.63)
Cardiac	63	44	69.8	19	30.2	1.12 (0.74 - 1.68)
Malignancy	55	43	78.2	12	21.8	0.77 (0.46 - 1.31)
Tuberculosis	39	25	64.1	14	35.9	1.35 (0.86 - 2.11)
Hematologic	16	16	100.0	0	0.0	-
Metabolic	16	10	62.5	6	37.5	1.38 (0.72 - 2.66)
Hepatic	5	4	80.0	1	20.0	0.73 (0.12 - 4.23)
Immunodeficiency	4	3	75.0	1	25.0	0.91 (0.17 - 5.01)
Labs						
Procalcitonin >0.05	207	112	54.1	95	45.9	2.35 (1.59 - 3.47)**
WBC <4.5	40	24	60.0	16	40.0	1.55 (0.98 - 2.44)[+]
WBC >11	235	172	73.2	63	26.8	1.04 (0.74 - 1.44)
Platelet <150	92	60	65.2	32	34.8	1.39 (0.98 - 1.97)[+]
Platelet >450	86	62	72.1	24	27.9	1.12 (0.75 - 1.66)
D-dimer >0.5	208	101	48.6	107	51.4	1.80 (0.78 - 4.17)
Ferritin <17.9	6	3	50.0	3	50.0	1.14 (0.50 - 2.60)
Ferritin >464	82	35	42.7	47	57.3	1.30 (0.99 - 1.72)[+]

[a] Numbers may not sum to the total sample size due to missing data.
CI: confidence interval; RR: Rate Ratio; WBC: x 10^9/L; Platelet 10^9/L; Procalcitonin ng/ml; Ferritin: ng/ml, D-dimer ug/ml; LDH: U/L
*[+]p<0.10; *p<0.05; **p<0.001.*

incidentally on PCR, which was performed on admission to guide patient placement and cohorting.

In this study, most cases were classified as mild, consistent with findings from previous studies.[19] Patients were initially admitted for reasons other than COVID-19, such as acute abdomen, burn, and trauma. These comprised nearly 20% of all COVID-19 admissions in the pediatric unit of the hospital. Other medical reasons for admission include chemotherapy, status epilepticus, diabetic ketoacidosis, blood or albumin transfusion.

The PGH was declared a COVID-19 referral center at the start of the pandemic on March 30, 2020 hence, severe and critical patients from other hospitals were prioritized and managed, especially those requiring intensive care. Patients with severe and critical COVID-19 illness comprised more than a quarter of total admissions. Most have comorbidities and underlying conditions. These cases were given remdesivir, tocilizumab and corticosteroids.

Presenting symptoms among hospitalized patients with COVID-19 in this study were similar to other studies where fever and cough were the predominant symptoms in children. Diarrhea, vomiting, rhinorrhea, sore throat, headache, and fatigue were not as common, occurring in only 10-20% of children which may not require hospitalization.[5,20]

Although respiratory involvement is most common in patients with COVID-19, the virus can affect other organ systems due to systemic inflammation induced by the disease along with multisystem expression of Angiotensin Converting Enzyme 2 (ACE2) receptors which permits viral entry into cells. This explains the extrapulmonary symptoms

Table 9. Crude Associations between Covariates and Mortality among Filipino Pediatric Patients Admitted for COVID-19[a]

Characteristic	Total n	Survivors		Non-Survivors		Crude HR (95% CI)
		n 408	% 91.1	n 40	% 8.9	
Age						
<1	91	81	89.0	10	11.0	1.21 (0.53 – 2.75)
1 – 5	116	103	88.8	13	11.2	1.33 (0.62 - 2.88)
6 – 10	79	75	94.9	4	5.1	0.66 (0.21 - 2.02)
11 – 19	162	149	92.0	13	8.0	Ref (1.00)
Sex						
Male	263	240	91.3	23	8.8	Ref (1.00)
Female	185	168	90.8	17	9.2	1.03 (0.55 - 1.93)
Presenting Symptoms						
Shortness of breath	119	94	79.0	25	21.0	3.42 (1.79 - 6.54)**
Fever	199	176	88.4	23	11.6	1.55 (0.83 - 2.90)
Cough	128	110	85.9	18	14.1	1.77 (0.95 - 3.30)+
Vomiting/nausea	82	72	87.8	10	12.2	2.00 (0.97 - 4.12)+
Diarrhea	58	52	89.7	6	10.3	1.38 (0.58 - 3.29)
Coryza/colds	54	49	90.7	5	9.3	1.05 (0.41 - 2.68)
Comorbidities						
Any comorbidity	371	338	91.1	33	8.9	0.73 (0.32 – 1.67)
Surgical/Traumatic	72	72	100.0	0	0.0	-
Neurologic	65	61	93.9	4	6.2	0.51 (0.18 - 1.43)
Cardiac	63	56	88.9	7	11.1	1.18 (0.52 - 2.67)
Malignancy	55	49	89.1	6	10.9	1.09 (0.46 - 2.60)
Congenital anomaly	50	46	92.0	4	8.0	0.70 (0.25 - 1.97)
Tuberculosis	39	34	87.2	5	12.8	0.98 (0.38 - 2.51)
Lung disease	24	21	87.5	3	12.5	1.16 (0.36 - 3.76)
Hematologic	16	15	93.8	1	6.3	1.02 (0.14 - 7.46)
Metabolic	16	13	81.3	3	18.8	2.39 (0.73 - 7.76)
Hepatic	5	4	80.0	1	20.0	2.28 (0.31 - 16.60)
Immunodeficiency	4	4	100.0	0	0.0	-
Labs						
Platelet <150	92	78	84.8	14	15.2	2.04 (1.04 - 4.00)*
Procalcitonin >0.05	207	176	85.0	31	15.0	2.30 (1.06 - 5.00)*
WBC <4.5	40	34	85.0	6	15.0	1.58 (0.62 - 4.04)
WBC >11	235	217	92.3	18	7.7	0.73 (0.37 - 1.44)
Platelet >450	86	82	95.4	4	4.7	0.55 (0.19 - 1.59)
D-dimer >0.5	208	177	85.1	31	14.9	-
Ferritin <17.9	6	6	100.0	0	0.0	-
Ferritin >464	82	64	78.1	18	22.0	1.80 (0.86 - 3.76)

[a] Numbers may not sum to the total sample size due to missing data.
CI: confidence interval; HR: Hazard Ratio; WBC: x 10^9/L; Platelet 10^9/L; Procalcitonin ng/ml; Ferritin: ng/ml, D-dimer ug/ml; LDH: U/L
*+p<0.10; *p<0.05; **p<0.001.*

involving the gastrointestinal, cardiovascular, hematologic, renal, musculoskeletal, and endocrine systems.[21]

MIS-C cases comprised less than 3% of admitted cases, notably in the 1-5-year age group with majority having no underlying comorbidities. Although earlier reports of MIS-C showed that only 35% of patients had comorbidities, a more recent large-scale cohort in Sweden and meta-analysis found that MIS-C was associated with respiratory (asthma) and neurologic diseases. Obesity as a risk factor remains inconclusive, as studies have contrasting results as to the impact of body weight on this disease. Our data present a younger cohort of patients, with international and published local data reporting more cases in the 5-11-year age group, which may be due to the smaller number of MIS-C patients.[22,23]

Several studies have also reported cases in children with a current or recent infection with SARS-CoV-2 presenting with a severe inflammatory syndrome with Kawasaki disease-like features.[24] In this study, the presence of fever, rash, gastrointestinal symptoms of diarrhea and vomiting, and cough suggested the presence of MIS-C, similar to findings in other MIS-C patients worldwide.[23]

Laboratory tests may aid in the screening of children with COVID-like symptoms, anticipate the need for further management, and assess response to therapy.[25] As COVID-19 induces systemic inflammation, this impacts on the process of hematopoiesis and even hemostasis. During early disease, normal or decreased leukocyte and lymphocyte counts can occur[26] although in this study, more than half of patients had elevated WBC. Our result may be different from

findings in literature, where a normal WBC is usually the most common finding among children with COVID-19.[27] Leukocytosis in COVID-19 patients may suggest a bacterial infection or a superinfection. Alternatively, this may also be explained by many surgical, traumatic, and cancer patients in this cohort. Other studies also identified a variety of hematological abnormalities such as lymphopenia and leukopenia.[27,28] The findings in this study did not observe a trend for low lymphocyte counts in children with severe and critical COVID-19. In adults, low lymphocyte counts were associated with the development of ARDS, the need for critical care, and mortality.[29] Pronounced lymphopenia was associated with severe COVID-19 and is seen as the disease progresses.[30]

The Inflammatory markers C-reactive protein (CRP), procalcitonin, D-dimer, creatine kinase (CK), lactate dehydrogenase (LDH), interleukin-6 (IL-6), and ferritin are biomarkers that may be used in COVID-19.[25] CRP was elevated in 14-54% of COVID-19 patients in a meta-analysis that included 334,398 children and adolescents.[20] The proportion of elevated CRP in this meta-analysis was lower compared to our study, where 70% of available results had CRP >6, with as many as 80-83% of severe and critical cases having elevated markers. The marked increase in CRP in this study may be explained by the fact that majority of asymptomatic and mild cases did not have a CRP done, thus reflecting a cohort with more CRP samples obtained for severe and critical cases. Similar trends were seen in procalcitonin, ESR, ferritin, LDH, and IL-6, where elevated markers were seen in severe and critical COVID-19. This conforms with findings that higher values were associated with disease severity.[25,31,32] However, unlike other studies that showed that only 25-50% of children with COVID-19 present with elevated procalcitonin, our cohort showed a larger proportion of patients with PCT elevation, which may be due to severe inflammation and may also suggest the presence of a bacterial co-infection.[32–35]

Apart from its effect on inflammatory markers, COVID-19 also affects the hemostatic system. These coagulation abnormalities can manifest as thrombocytopenia, prolonged prothrombin time (PT), low serum fibrinogen level, and raised D-dimer. Although this constellation of findings suggests the development of Disseminated Intravascular Coagulation (DIC), the pattern seen in COVID-19 is noticeably different compared to that of sepsis, which has a more profound thrombocytopenia and less elevated D-dimer levels.[36,37] Congruent with other studies in children, D-dimer, the most typical finding in COVID-19 coagulopathy, was the most frequently elevated laboratory parameter in our study.[20,36]

Imaging studies related to COVID-19 in children have been evaluated in several studies to date. Normal chest radiographs were most common in asymptomatic and mild COVID-19 patients in our study, and abnormal findings were mostly seen in patients with moderate, severe, and critical disease. Apart from normal chest radiographs, the most common finding seen in chest radiographs of COVID-19 were opacities.[27,38,39] Chest tomography findings in this study were also consistent with data from other institutions. Ground-glass opacities were the most common finding, with bilateral peripheral and central as the most frequent distribution.[39,40]

As to COVID-19 treatment, to date, there is still evolving data on the treatment and prevention of COVID-19 in adults and children. Antiviral agents are recommended only in severe/critical cases and has limited indications for certain age groups.

Currently, remdesivir, with antiviral activity against SARS-CoV-2, is the only Food and Drug Administration-approved therapeutic agent for children with COVID-19 aged ≥12 years and weigh ≥40 kg. This is also available for use in younger children (weight>3.5 kg to up to <40kg) through an FDA Emergency Use Authorization. The control of the hyperreactive inflammatory effects of SARS-CoV-2, through agents that modulate the immune response, are also used in severe to critical COVID-19. These are also human blood-derived products and immunomodulatory therapies. These products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., immunoglobulin, convalescent plasma). Their effects are proposed to have either direct antiviral properties or immunomodulatory effects.[10,41,42] When the COVID-19 pandemic was initially declared, there were no guidelines and options for treatment were very limited. The use of convalescent plasma was one early treatment option used in our institution due to limited age indications for the other drugs and the plasma became available under emergency use. Thus, seven pediatric patients classified as severe cases were able to receive it and all improved or recovered from COVID-19 illness.

Corticosteroid treatment, particularly dexamethasone, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the most significant effect observed in patients who require mechanical ventilation.[39] The Infectious Disease Society of America (IDSA) guidelines on the treatment and management of patients with COVID-19, the NIH guidelines, and our local guidelines strongly recommend its use in this setting. If dexamethasone is unavailable, an alternative glucocorticoid (i.e. prednisone and methylprednisolone) were used.[10,42,43]

The management of patients in this retrospective cohort adhered to existing treatment guidelines available at the time of patient's admission. Asymptomatic and mild cases were given supportive treatment and medications, while investigational drugs and antibiotics if needed were given to severe and critical cases.

Antibiotics were given to the majority of patients at the outset. The decision to start a patient on an antibiotic in a patient with severe COVID-19 becomes a judgment call for the clinician. Of note is that antibiotics were discontinued when a bacterial cause of the infection was not considered

by clinical and laboratory evaluations. There are equally important supportive modalities recommended in the management of severe to critical pediatric COVID-19 which include temporizing hemodynamics in cases of shock, providing adequate oxygenation and ventilation, renal replacement therapy, and observance of infection control measures.[41] Complications from COVID-19 documented were the occurrence of nosocomial infection, shock, renal injury, hepatic injury, and myocarditis. These were seen in majority of patients with severe and critical COVID-19. Only a few patients developed thrombus formation.

SARS-CoV-2 was identified as a strong risk factor for the development of nosocomial infection during the COVID-19 pandemic. Other identified risk factors for hospital-acquired infections were chronic comorbidities, intensive care unit stay, hospital type, and extremes of BMI.[44] The combination of these risk factors may explain the high incidence of nosocomial infection in this study. Other complications were less common in children.[45]

Renal injury results from hypoxia, cytokine storm, rhabdomyolysis, nephrotoxic drugs, and superimposed infection.[46,47] Liver dysfunction is likely secondary to the use of hepatotoxic drugs, hypoxia-induced liver injury, systemic inflammation, and multi-organ failure.[48] Cardiac complications occur due to cardiac strain from hypoxia and respiratory failure, direct effect of SARS-CoV-2 on the heart, result of inflammation and cytokine storm, metabolic derangements, or consequences of drugs used for treatment.[49–51]

Several theories have been postulated to explain why COVID-19 presents mildly in children and why complications are less common. However, these mechanisms are not yet fully understood. The difference in severity between adults and children has been suggested to emerge from two main categories: factors that increase the risk of COVID-19 in adults and factors that protect children from COVID-19. These proposed protective factors include (1) age-related differences in immune response, (2) recurrent and concurrent infections, particularly viral and mycoplasma infections, (3) exposure to commonly circulating human coronaviruses, (4) colonizing microbial flora, (5) higher melatonin levels, which has anti-inflammatory and anti-oxidative properties, (6) off-target effects of live vaccines, and (7) intensity of viral exposure.[19,45]

Contrary to findings in literature,[52] this study showed that the presence of any comorbidity except lung disease and congenital anomalies were less likely to progress to severe COVID-19. This may be because a large proportion of underlying conditions were surgical or trauma patients who were admitted for surgical management. The designation of the hospital as a COVID-19 tertiary referral center led to admissions that had COVID-19 as an incidental finding. The presence of underlying neurologic, cardiac, and chronic lung disease was cited in the literature as risk factors for severe COVID-19 in children.[52-54] However, for this study, only underlying lung disease and congenital anomalies were identified risk factors. The presence of shortness of breath, fever, cough, diarrhea and colds increased the rate of severe disease. Shortness of breath on admission was also a predictor of severe disease in other studies.[6]

Adverse events from treatment documented in this study were anaphylaxis from IVIG and rash with the administration of remdesivir. Although anaphylaxis from IVIG is rare, the pediatric age group was more likely to develop this complication compared to adults.[55] Rash is not a common occurrence resulting from the administration of remdesivir. Adverse events usually associated with remdesivir are acute kidney injury, constipation, increased alanine transaminase, hyperglycemia, hypertension, pyrexia, and anemia, which were not found in our study.[56]

Limitations

This study has several limitations. There are missing information encountered during chart review which may contribute to the unknown results. This study is limited to the epidemiology of COVID-19 infection in children in the population involved which only looked into hospitalized patients until June 2022.

CONCLUSION

Most patients in this cohort had a favorable outcome as the PGH is a tertiary COVID-19 referral center where the investigational drugs were available, complete with subspecialists and is fully equipped to provide intensive and comprehensive care to critically ill patients. Admitted pediatric COVID-19 cases are generally mild but admission is due to underlying illness or comorbidities, and those with severe to critical cases have underlying comorbidities and had either progression or complications due to Covid disease. The use and availability of corticosteroids and remdesivir for COVID-19 management may have an impact on the favorable outcome of most of the patients. D-dimer, LDH, IL-6, ferritin, and procalcitonin were elevated among severe and critical cases which can be utilized as inflammatory markers. The high proportion of mild cases and low case fatality rate support that COVID-19 is generally mild in children.

Recommendations

A continuation of data collection until admissions in 2023 is needed to get a more comprehensive view of COVID-19 in a tertiary referral center. A multicenter study involving pediatric patients from both urban and rural centers may also provide better insight in the diagnosis and management of COVID-19 infection in children.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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APPENDIX

COVID-19 Disease Severity

Adapted from the Pediatric Infectious Disease Society of the Philippines[10]

Asymptomatic – Patients with no symptoms of COVID-19 but tested positive in SARS-CoV-2 RT PCR.

Mild – Symptomatic patients meeting the case definition for COVID-19-patients with uncomplicated respiratory tract symptoms may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache without evidence of viral pneumonia or hypoxia.

Moderate – Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia, including SpO_2 ≥95% on room air

Severe – Child with cough or difficulty in breathing, plus at least one of the following:

a. Central cyanosis or SpO_2 <90%
b. Severe respiratory distress (e.g., grunting, chest indrawing)
c. Signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
d. Other signs of pneumonia may be present: chest indrawing, fast breathing (in breaths/min): <2 months, ≥60 2–11 months, ≥50 1–5 years, ≥40.

Critical

1. **Septic shock:** any hypotension (SBP <5th centile or >2 SD below normal for age) or 2-3 of the following:
   a. Altered mental state
   b. Tachycardia (HR >160 bpm in infants or >150 bpm in children) or bradycardia (HR <90 bpm in infants or <70 bpm in children)
   c. Prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses
   d. Tachypnea
   e. Mottled skin or petechial or purpuric rash
   f. Increased lactate
   g. Oliguria
   h. Hyperthermia or hypothermia

2. **Acute Respiratory Distress Syndrome:** Onset was within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms; Chest imaging with bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules; respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. ECG) to exclude hydrostatic cause of infiltrates / edema if no risk factor present; presence of oxygen impairment

3. **Sepsis**: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count

4. **Acute thrombosis:** acute venous thromboembolism, acute coronary syndrome, acute stroke
   Multisystemic Inflammatory Syndrome in Children (MIS-C) –
   a. children and adolescents 0–19 years of age with fever >3 days **AND**
   b. two of the following: rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers), acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain); **AND**
   c. elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. **AND**
   d. no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. **AND**
   e. evidence of COVID-19 (RT- PCR, antigen test or serology positive), or likely contact with patients with COVID-19.