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ORIGINAL ARTICLE

SARS-CoV-2 INFECTION IN FILIPINO CHILDREN: AN INTERIM REPORT FROM THE SALVACION REGISTRY

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ABSTRACT

Background: The COVID-19 pandemic continues to afflict nations worldwide. The Philippines is no exception which has recorded more than 3 million cases as of December 2021 with children comprising 12% of total cases. Since the start of the pandemic, the Pediatric Infectious Disease Society of the Philippines (PIDSP) has been collecting data nationwide, through an online pediatric COVID-19 registry (SALVACION registry), to provide a better understanding of COVID-19 in children in the local setting.

Methods: This was an ambispective cohort study of pediatric COVID-19 cases in the Philippines reported from March 2020 to December 2021. Data on clinical features, laboratory findings, disease severity, and treatment outcomes were voluntarily reported by physicians across the country. This study was approved by the Department of Health Single Joint Research Ethics Board.

Results: As of December 30, 2021, there were 2,127 cases reported in the registry, with a median age of 5 years (interquartile range: 1-13 years) and mostly mild (41.9%) or moderate (24.5%) in severity. The top symptoms reported were fever (57.9%), cough (42.7%), coryza/colds (29.4%), anorexia (25.2%), and difficulty of breathing (23.1%). The most common comorbidities were hematologic-oncologic diseases (7.4%), neurologic diseases (7.0%) and surgical conditions (4.4%), while the most common co-infections were sepsis (6.3%), dengue fever (4.8%) and healthcare-associated pneumonia (2.1%). Significantly higher median CRP, procalcitonin, D-dimer, ferritin, transaminases and lactate dehydrogenase were seen among severe/critical cases compared to non-severe cases. There was a high frequency of antibiotic use (58%). Most cases recovered, although 172 deaths were reported with an 8.6% case fatality rate. The most common comorbidities in those who died were neurologic (15.7%), cardiac (12.8%) and hematologic (11.6%) diseases.

Conclusion: Children across all age groups are susceptible to COVID-19 and most cases are mild or moderate in severity. Among severe and critical cases, the most common comorbidities were neurologic, hematologic-oncologic and cardiac diseases. Most patients recovered with supportive management.

KEYWORDS: *COVID-19, SARS-CoV-2, Child, Registry, Philippines, Pediatric Multisystem Inflammatory Disease*, *COVID-19 related*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that all authors have met the requirements for authorship.

INTRODUCTION

The novel Coronavirus disease 2019 (COVID-19) pandemic is a global health threat of unprecedented magnitude. Worldwide, as of April 19, 2022, there have been 503,131,834 reported cases and 6,200,571 deaths. The Western Pacific region has accounted for over 50 million cases, with about 20% reported in the pediatric population.[1]

SARS-CoV-2 causes an acute respiratory infection with varying severity across different age groups. The elderly and persons with comorbidities tend to have severe disease, while children are relatively spared.[2] There are, however, reports of severe to critical cases in the pediatric population with unusual manifestations described as Multisystem Inflammatory Syndrome in Children (MIS-C).

Infections in the younger age group is expected to increase due to the growing number of infections in adults and partly because younger children have challenges in practicing minimum public health standards. Although the true incidence of COVID-19 in children is unknown due to lack of widespread testing and priority in testing adults and those with severe illness, a systematic review by Ludvigsson showed that children have so far accounted for 1-5% of diagnosed COVID-19 cases with mild disease and fewer deaths. Fever and respiratory symptoms were prevalent among symptomatic children and only a few developed severe pneumonia with elevated inflammatory markers.[4] Another review by Zimmermann showed that 83% of children with COVID-19 had a positive contact history, with a mean incubation period of 7 days. Co-infections were reported in up to 79% of children (mainly with *Mycoplasma sp.* and influenza), and up to 35% were asymptomatic.[5] An epidemiological study of pediatric COVID-19 infection across Asia demonstrated that risk factors for severe disease were age younger than 12 months, presence of comorbidities and cough at presentation, with an overall mortality of 2.3%.[6]

In several epidemiological studies of this disease, the pediatric population seems underrepresented with low death rates. A multicenter study in Europe involving 582 children in 25 countries described a case fatality rate of 0.69%.[3]

As of May 13, 2022, the Philippines has reported 3,687,748 COVID-19 cases, with the pediatric age group (less than 19 years old) accounting for 12% of cases.[7] To date, there is no published data on the epidemiology of COVID-19 in the Filipino pediatric population. Blasurca, *et al.* published a case series of 5 pediatric patients with MIS-C[8] and a case report of fulminant hepatitis secondary to SARS-CoV-2.[9] These reports of severe manifestations of COVID-19 in children are probably outliers in the more than 150,000 cases of COVID-19 in children in the Philippines. A local study by Po, *et al.* also looked into the outcomes of infants born to mothers with SARS-CoV-2 infection, and it showed that none of the infants had COVID-19.[10] With the scarcity of data on pediatric COVID-19 in the Philippines, the Pediatric Infectious Disease Society of the Philippines created an online registry for the surveillance and analysis of COVID-19 in children nationwide (SALVACION Registry). This study aimed to look into the clinical profile of COVID-19 among Filipino children and describe the diagnostic and therapeutic management in the pediatric population.

MATERIALS AND METHODS

This is an ambispective cohort study of patients 0 to 18 years old diagnosed with COVID-19 in the Philippines and reported to the SALVACION Registry from March 2020 to December 31, 2021. The SALVACION Registry is a web-based pediatric COVID-19 registry developed by the UP-NIH National Telehealth Center in collaboration with the SALVACION Team of PIDSP and supported by the Philippine Pediatric Society (PPS).

Physicians from both government and private institutions voluntarily uploaded to the SALVACION registry website the data of their pediatric patients with probable or confirmed COVID-19 admitted in the hospital or seen at their respective outpatient departments.

The following data were submitted: reporting institution, demographic information, exposure history, comorbidities, co-infections, clinical presentation, laboratory and imaging results, treatment regimen and outcome. Neither identity nor personal data were collected for the study.

Classification of patients as confirmed or probable COVID-19 was based on the definitions provided in the PPS-PIDSP Interim Guidelines on the Screening, Assessment and Clinical Management of Pediatric Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) Version 4, February 6, 2021 published in the PIDSP Journal. Cases were classified as "non-severe" if they presented with mild or moderate features based on the guideline, and "severe" if they presented with severe and critical features.

This study adhered to the ethical considerations and principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethics Guidelines for Health Research. The study was reviewed and approved by the DOH Single Joint Research Ethics Board (SJREB-2020-40).

Data Analysis

Descriptive statistics were used for categorical variables and expressed as frequencies and percentages. Shapiro-Wilk test was used to determine the normality assumption of continuous variables. Continuous quantitative data that met normality assumptions were summarized using mean and standard deviation (SD), while those that did not were described using median and range.

An independent t-test was used to compare means between severe and non-severe pediatric cases for continuous variables.

The Mann-Whitney U test was used if the data were not normally distributed. For categorical variables, the chi-square test was used to compare the outcomes. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at a 0.05 α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

The registry collected 2,127 pediatric cases of COVID-19 from March 2020 to December 2021.

The median age of patients was 5 years (interquartile range: 1-13 years). Most cases were in the 1 to 5-year age group (26.2%), followed by the 11 to 15-year age group (20.8%). Males comprised 57.12% of cases. As to disease severity, patients were predominantly classified as mild (41.9%) and moderate (24.5%). There were 363 (17.1%) asymptomatic cases and 16 (0.7%) with MIS-C. Of the reported patients, 89.5% were hospitalized. There were 62 reports which were excluded (unverified age and unknown severity), resulting in 2,065 patients for this study (Table 1).

Table 1. Demographic and clinical characteristics of confirmed COVID-19 pediatric patients in the SALVACION registry *(n = 2,065)*

Parameter		Frequency (%)
Age	Unknown/Unverified	52 (2.44)
	0-30 days old	174 (8.18)
	1 mo - <1 yr	318 (14.95)
	1 – 5 yr	558 (26.23)
	6 – 10 yr	342 (16.08)
	11 – 15 yr	442 (20.78)
	16 – 18 yr	241 (11.33)
Sex	Unknown/Unverified	3 (0.14)
	Male	1215 (57.12)
	Female	909 (42.74)
Severity	Unknown/Unverified	10 (0.47)
	Asymptomatic	363 (17.07)
	Mild	892 (41.94)
	Moderate	521 (24.49)
	Severe	169 (7.95)
	Critical	156 (7.33)
	MIS-C	16 (0.75)
Admission Status	Hospitalized	1904 (89.52)
	Not hospitalized	223 (10.48)

Children below 1 year of age comprised 33.13% and 41.06% of those with severe and critical diseases, respectively. All cases of MIS-C were between 1 to 15 years old, with most cases in the 6 to 10-year age group (43.7%). The most common pre-existing conditions reported were hematologic-oncologic diseases (7.4%), neurologic diseases (7.0%) and surgical conditions (4.4%). Among severe and critical cases, the most common comorbidities were neurologic diseases (14.5% and 14.6%), hematologic-oncologic diseases (11.4% and 7.9%) and cardiac diseases (9.0% and 8.6%).

Among children with MIS-C, pre-existing conditions identified were obesity (n=3), acute appendicitis (n=1) and concomitant intestinal amoebiasis (n=1) (Table 2).

Top symptoms reported were fever (57.9%), cough (42.7%), coryza/colds (29.4%), anorexia (25.2%) and difficulty of breathing (23.1%) which was also the most common symptom among severe and critical patients (69%). The most common co-infections were sepsis (6.3%), dengue fever (4.8%), healthcare-associated pneumonia (2.1%) and tuberculosis (1.5%) (Table 2).

Table 2. Clinical characteristics according to disease severity

Parameter		Total (n=2065)	Asymp-tomatic (n=353)	Mild (n=872)	Moderate (n=507)	Severe (n=166)	Critical (n=151)	MIS-C (n=16)
		Frequency (%)						
Age	<30 days	172 (8.33)	50 (14.16)	29 (3.33)	51 (10.06)	18 (10.84)	24 (15.89)	0
	1 – 11 months	316 (15.3)	37 (10.48)	96 (11.01)	108 (21.3)	37 (22.29)	38 (25.17)	0
	1 – 5 years	556 (26.92)	83 (23.51)	252 (28.9)	145 (28.6)	32 (19.28)	40 (26.49)	4 (25.0)
	6 – 10 years	340 (16.46)	58 (16.43)	165 (18.92)	67 (13.21)	28 (16.87)	15 (9.93)	7 (43.75)
	11 – 15 years	441 (21.36)	72 (20.4)	223 (25.57)	87 (17.16)	30 (18.07)	24 (15.89)	5 (31.25)
	16 – 18 years	240 (11.62)	53 (15.01)	107 (12.27)	49 (9.66)	21 (12.65)	10 (6.62)	0
Pre-existing conditions	Obesity	68 (3.29)	4 (1.13)	13 (1.49)	25 (4.93)	19 (11.45)	4 (2.65)	3 (18.75)
	Bronchial asthma	54 (2.62)	3 (0.85)	23 (2.64)	17 (3.35)	7 (4.22)	4 (2.65)	0
	Tuberculosis	31 (1.50)	2 (0.57)	8 (0.92)	12 (2.37)	5 (3.01)	4 (2.65)	0
	Other respiratory conditions	27 (1.31)	2 (0.85)	2 (0.46)	4 (0.99)	10 (6.02)	11 (7.28)	0
	Cardiac disease	77 (3.73)	5 (1.42)	17 (1.95)	27 (5.33)	15 (9.04)	13 (8.61)	0
	Hematologic disease	152 (7.36)	23 (6.52)	61 (7)	37 (7.3)	19 (11.45)	12 (7.95)	0
	Kidney disease	63 (3.05)	8 (2.27)	16 (1.83)	21 (4.14)	11 (6.63)	7 (4.64)	0
	Neurologic disease	145 (7.02)	14 (3.97)	41 (4.82)	45 (8.88)	23 (14.46)	22 (14.57)	0
	Prematurity	44 (2.13)	2 (0.57)	4 (0.46)	14 (2.76)	11 (6.63)	13 (8.61)	0
	Pregnancy	12 (0.58)	2 (0.57)	3 (0.34)	4 (0.79)	1 (0.6)	2 (1.32)	0
	Smoking	4 (0.19)	0	2 (0.23)	0	2 (1.2)	0	0
	Gastrointestinal disorders	34 (1.65)	5 (1.42)	16 (1.83)	5 (0.99)	3 (1.81)	5 (3.31)	1 (6.25)
	Surgical GI conditions	91 (4.41)	30 (8.5)	33 (3.78)	19 (3.75)	4 (2.41)	4 (2.65)	1 (6.25)
	Genetic/Metabolic	32 (1.55)	2 (0.57)	12 (1.26)	7 (1.38)	4 (1.81)	7 (4.64)	0
	Endocrinologic	16 (0.77)	3 (0.85)	6 (0.69)	2 (0.39)	4 (2.41)	1 (0.66)	0
	Rheumatologic	10 (0.48)	2 (0.57)	4 (0.46)	2 (0.39)	2 (1.2)	0	0
	Allergic disease	18 (0.87)	0	10 (0.92)	6 (1.18)	2 (1.2)	0	0
	Immunodeficiency	3 (0.15)	1 (0.28)	1 (0.11)	0	1 (0.6)	0	0
	Psychiatric	2 (0.1)	1 (0.28)	0	1 (0.2)	0	0	0
	Malnutrition	19 (0.92)	1 (0.28)	7 (0.8)	6 (1.18)	3 (1.81)	2 (1.32)	0
Symptoms	Fever	992 (57.94)	-	472 (54.13)	312 (61.54)	113 (68.07)	79 (52.32)	16 (100)
	Cough	731 (42.70)	-	303 (34.75)	261 (51.48)	98 (59.04)	66 (43.71)	3 (18.75)

Parameter		Total (n=2065)	Asymp-tomatic (n=353)	Mild (n=872)	Moderate (n=507)	Severe (n=166)	Critical (n=151)	MIS-C (n=16)
		Frequency (%)						
Symptoms (cont.)	Coryza/Colds	503 (29.38)	-	268 (30.73)	153 (30.18)	52 (31.33)	28 (18.54)	2 (12.5)
	Difficulty of breathing	396 (23.13)	-	36 (4.13)	136 (26.82)	114 (68.67)	105 (69.54)	5 (31.25)
	Sore throat	118 (6.89)	-	74 (8.49)	26 (5.13)	11 (6.63)	5 (3.31)	2 (12.5)
	Watery stools	250 (14.60)	-	121 (13.88)	84 (16.57)	22 (13.25)	15 (9.93)	8 (50)
	Vomiting	322 (18.81)	-	172 (19.72)	94 (18.54)	26 (15.66)	21 (13.91)	9 (56.25)
	Poor suck/decreased appetite	431 (25.18)	-	130 (14.91)	146 (28.8)	68 (40.96)	75 (49.67)	12 (75)
	Seizure	152 (8.88)	-	49 (5.62)	59 (11.64)	19 (11.45)	24 (15.89)	1 (6.25)
	Muscle pain	90 (5.26)	-	52 (5.96)	19 (3.75)	11 (6.63)	5 (3.31)	3 (18.75)
	Loss of smell	71 (4.15)	-	50 (5.73)	19 (3.75)	2 (1.2)	0	0
	Loss of taste	54 (3.15)	-	35 (4.01)	17 (3.35)	1 (0.6)	1 (0.66)	0
	Abdominal pain	242 (14.14)	-	123 (14.11)	70 (13.81)	23 (13.86)	18 (11.92)	8 (50)
	Headache	52 (3.04)	-	34 (3.9)	10 (1.97)	5 (3.01)	2 (1.32)	1 (6.25)
	Rash	37 (2.16)	-	18 (2.06)	11 (2.17)	1 (0.6)	0	7 (43.75)
	Oral and conjunctival mucosal changes	13 (0.76)	-	4 (0.46)	4 (0.79)	0	0	5 (31.25)
	Chest pain	12 (0.70)	-	4 (0.46)	5 (0.99)	2 (1.2)	1 (0.66)	0
	Epistaxis	12 (0.70)	-	6 (0.69)	3 (0.59)	3 (1.81)	0	0
Concurrent Infections	Influenza	7 (0.34)	0	6 (0.69)	0	1 (0.6)	0	0
	Dengue fever	99 (4.79)	2 (0.57)	56 (6.42)	24 (4.73)	12 (7.23)	5 (3.31)	0
	Tuberculosis	31 (1.50)	2 (0.57)	8 (0.92)	12 (2.37)	5 (3.01)	4 (2.65)	0
	Healthcare-associated pneumonia	44 (2.13)	3 (0.85)	9 (1.03)	5 (0.99)	15 (9.04)	12 (7.95)	0
	Sepsis	130 (6.30)	8 (2.27)	20 (2.29)	41 (8.09)	27 (16.27)	34 (22.52)	0
	Bacterial Meningitis	13 (0.63)	0	4 (0.46)	6 (1.18)	0	3 (1.99)	0
	Urinary tract infection	28 (1.36)	2 (0.57)	16 (1.83)	6 (1.18)	2 (1.2)	2 (1.32)	0
	Gastrointestinal infections	13 (0.63)	1 (0.28)	6 (0.69)	4 (0.79)	1 (0.6)	0	1 (6.25)
	Skin, soft tissue, musculoskeletal infections	15 (0.73)	2 (0.57)	6 (0.69)	5 (0.99)	1 (0.6)	1 (0.66)	0
	Viral exanthem	3 (0.15)	0	3 (0.34)	0	0	0	0
	Leptospirosis	3 (0.15)	0	0	2 (0.39)	1 (0.6)	0	0

Table 3 shows the laboratory findings of cases in the registry. There were significantly higher median CRP, procalcitonin, D-dimer, ferritin, transaminases and lactate dehydrogenase among severe/critical cases compared to non-severe cases.

Features of pneumonia were radiologically seen in 52.37% of cases. Among those with abnormal chest CT scan findings, bilateral peripheral ground glass opacities were the most commonly seen (48.72%).

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Table 3. Laboratory findings according to disease severity

Parameter		Total (n=2065)	Non-severe (n=1732)	Severe/Critical (n=317)	MIS-C (n=16)	*p value*
		Median (Range)				
Complete blood count	Hemoglobin	[N=1772] 127 (17-269)	[N=1462] 128 (22-265)	[N=294] 120 (17-269)	[N=16] 119.5 (84-148)	<.001
	Hematocrit	[N=1772] 0.38 (0.02-0.81)	[N=1462] 0.38 (0.02-0.8)	[N=294] 0.36 (0.07-0.81)	[N=16] 0.34 (0.24-0.43)	<.001
	WBC	[N=1773] 9.16 (0.1-99.99)	[N=1463] 8.82 (0.1-99.99)	[N=294] 11.15 (0.1-99.99)	[N=16] 12 (4.72-27)	<.001
	Segmented neutrophil	[N=1757] 0.56 (0.01-0.99)	[N=1454] 0.54 (0.01-0.99)	[N=288] 0.61 (0.01-0.96)	[N=15] 0.85 (0.44-0.95)	<.001
	Lymphocyte count	[N=1758] 0.34 (0.01-0.93)	[N=1454] 0.35 (0.01-0.93)	[N=289] 0.3 (0.01-0.91)	[N=15] 0.09 (0.01-0.45)	<.001
	Platelet	[N=1082] 300 (2-2745)	[N=890] 308 (5-2745)	[N=184] 255 (2-844)	[N=8] 181 (117-667)	<.001
Others	CRP	[N=799] 6 (0.02-576)	[N=623] 5 (0.02-576)	[N=160] 12 (0.1-292)	[N=16] 107 (6-508)	<.001
	Procalcitonin	[N=515] 0.28 (0.01-248)	[N=375] 0.16 (0.01-200)	[N=128] 1 (0.05-248)	[N=12] 16.165 (0.11-118.05)	<.001
	ESR	[N=184] 23.5 (0.03-289.22)	[N=143] 19 (0.03-289.22)	[N=30] 34.5 (2-135)	[N=11] 40 (7-110)	.319
	D-dimer	[N=157] 1.2 (0.1-22.51)	[N=73] 0.95 (0.1-17.31)	[N=79] 1.64 (0.12-22.51)	[N=5] 2.4 (1.87-10)	.024
	Ferritin	[N=233] 298 (1.63-30713)	[N=124] 176.5 (1.63-28058)	[N=100] 511.5 (7.8-30713)	[N=9] 712 (405-2907)	.088
	Aspartate aminotransferase	[N=233] 53.5 (1.07-5147.44)	[N=91] 37.5 (1.07-667.7)	[N=135] 73 (2-5147.44)	[N=7] 49 (14.1-125)	.002
	Alanine aminotransferase	[N=251] 37 (1.1-2919)	[N=99] 27 (1.1-334.3)	[N=145] 43 (1.64-2919)	[N=7] 53 (16.6-167)	.007
	Lactate dehydrogenase	[N=206] 436.5 (7.55-10483)	[N=118] 365.62 (7.55-5564)	[N=82] 617 (78-10483)	[N=6] 345.45 (282-507)	<.001
	Creatine kinase	[N=80] 53.7 (0.15-11397)	[N=31] 30.29 (0.15-1528)	[N=47] 68 (4.7-11397)	[N=2] 21.5 (15-28)	.073
	IL-6	[N=77] 111 (1.99-4325)	[N=24] 91.5 (2-1296)	[N=53] 120 (1.99-4325)	-	.225
	Troponin I ng/ml	0.0275 (0.007-1.8)	[N=2] 0.0275 (0.025-0.03)	[N=2] 0.9035 (0.007-1.8)	-	
	Pro-BNP pg/ml	89.76 (34.71-5,352)	86.1	[N=2] 834.88 (89.76-1580)	-	
	CK-MB U/L	72.6 (14.5-150)	[N=4] 47.495 (14.5-72.6)	134 (108.8-150)	-	
CXR findings	Normal X-ray findings	804 (47.63)	741 (53.73)	58 (19.8)	5 (31.25)	
	Abnormal X-ray findings	884 (52.37)	638 (46.27)	235 (80.2)	11 (68.75)	

Parameter		Total (n=2065)	Non-severe (n=1732)	Severe/Critical (n=317)	MIS-C (n=16)	*p value*
		Median (Range)				
CXR findings (cont.)	No infiltrates	21 (2.38)	20 (3.13)	1 (0.43)	0 (0)	
	Localized infiltrates	386 (43.67)	301 (47.18)	78 (33.19)	7 (63.64)	
	Multilobar infiltrates	312 (35.29)	192 (30.09)	117 (49.79)	3 (27.27)	
	Pleural effusion	69 (7.81)	35 (5.49)	32 (13.62)	2 (18.18)	
	Others	199 (22.51)	142 (22.26)	53 (22.55)	4 (36.36)	
Chest CT scan findings	Normal chest CT scan findings	7 (8.24)	4 (9.76)	3 (6.98)	0 (0)	
	Abnormal chest CT scan findings	78 (91.76)	37 (90.24)	40 (93.02)	1 (100)	
	Bilateral peripheral ground-glass opacities	38 (48.72)	18 (48.65)	19 (47.5)	1 (100)	
	Unilateral peripheral ground-glass opacities	5 (6.41)	3 (8.11)	2 (5)	0 (0)	
	Multifocal or diffuse ground-glass opacities	12 (15.38)	5 (13.51)	7 (17.5)	0 (0)	
	Segmental or lobar consolidation	20 (25.64)	6 (16.22)	14 (35)	0 (0)	
	Pleural effusion	19 (24.36)	9 (24.32)	9 (22.5)	1 (100)	
	Others	25 (32.05)	11 (29.73)	14 (35)	0 (0)	
Chest Ultrasound findings	Abscess	0	0	0	0	
	Effusion	10 (83.33)	5 (100)	5 (71.43)	0	
	Others	3 (25)	0	3 (42.86)	0	
2D Echocardiography findings [N=5]	Myocardial dysfunction	-	-	-	2 (40)	-
	Coronary arteritis	-	-	-	1 (20)	-
	Pericardial effusion	-	-	-	3 (60)	-
ABG	pH	[N=189] 7.39 (6.9-7.62)	[N=44] 7.425 (7.22-7.62)	[N=143] 7.37 (6.9-7.6)	[N=2] 7.335 (7.27-7.4)	
	PaCO2	[N=188] 28.75 (9.4-99)	[N=44] 28 (10-50.5)	[N=142] 29 (9.4-99)	[N=2] 23.5 (23-24)	
	HCO3	[N=188] 18.2 (1.9-49)	[N=44] 18.8 (4.1-38)	[N=142] 18.05 (1.9-49)	[N=2] 15.75 (14-17.5)	
	PaO2	[N=188] 117.3 (18.8-345)	[N=44] 99 (18.8-345)	[N=142] 124 (21-327)	[N=2] 164.5 (126-203)	

Table 4 shows the treatment and outcomes of patients. Antibiotics were the most commonly used drugs, with 58% of patients receiving at least one type of antibiotic. Nutritional support with zinc sulfate (57.2%) and vitamin D (39.9%) were also commonly used. Among antivirals, remdesivir was used in 3.15% of patients. The frequency of corticosteroid use was 11%.

Most severe and critical COVID-19 patients were given antibiotics (94.32%), corticosteroids (38.17%) with dexamethasone being the most commonly used (80.99%), remdesivir (14.2%) and IVIG (11.36%). Most children did not receive any respiratory support (73.5%) while 9% were placed on invasive ventilation. There were 2,005 patients with final dispositions. Among these, 172 deaths were reported with an 8.6% case fatality rate.

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Most common comorbidities in those who died were neurologic (15.7%), cardiac (12.8%) and hematologic (11.6%) diseases (Figure 1).

Table 4. Treatment and outcomes according to disease severity

Parameter		Total (n=2065)	Non-severe (n=1732)	Severe/Critical (n=317)	MIS-C (n=16)
		Frequency (%)			
Treatment	Hydroxychloroquine	8 (0.39)	5 (0.29)	3 (0.95)	0
	Lopinavir-Ritonavir	6 (0.29)	4 (0.23)	2 (0.63)	0
	Remdesivir	65 (3.15)	19 (1.1)	45 (14.2)	1 (6.25)
	Interferon	5 (0.24)	4 (0.23)	1 (0.32)	0
	Oseltamivir	10 (0.48)	8 (0.46)	2 (0.63)	0
	Tocilizumab	5 (0.24)	2 (0.12)	3 (0.95)	0
	Enoxaparin	2 (0.1)	0	2 (0.63)	0
	Antibiotics	1,198 (58.01)	883 (50.98)	299 (94.32)	16 (100)
	Azithromycin	402 (19.47)	302 (17.44)	96 (30.28)	4 (25)
	IVIG	68 (3.29)	17 (0.98)	36 (11.36)	15 (93.75)
	Convalescent plasma	6 (0.29)	2 (0.12)	4 (1.26)	0
	Corticosteroids	228 (11.04)	95 (5.48)	121 (38.17)	[N=12]
	Dexamethasone	182 (79.82)	80 (84.21)	98 (80.99)	4 (25)
	Methylprednisolone	27 (11.84)	4 (4.21)	15 (12.4)	8 (50)
	Hydrocortisone	21 (9.21)	10 (10.53)	11 (9.09)	0
	Zinc	1181 (57.19)	1016 (58.66)	156 (49.21)	9 (56.25)
	Vitamin D	825 (39.95)	695 (40.13)	122 (38.49)	8 (50)
Oxygen support	None	1518 (73.51)	1484 (85.68)	28 (8.83)	6 (37.5)
	Non-invasive	354 (17.14)	221 (12.76)	128 (40.38)	5 (31.25)
	Invasive MV	193 (9.35)	27 (1.56)	161 (50.79)	5 (31.25)
Outcome		[N=2005]	[N=1678]	[N=311]	[N=16]
	Discharged	1650 (82.29)	1493 (88.97)	145 (46.62)	12 (75)
	Death	172 (8.58)	21 (1.25)	148 (47.59)	3 (18.75)
	Transfer/HAMA	183 (9.13)	164 (9.77)	18 (5.79)	1 (6.25)

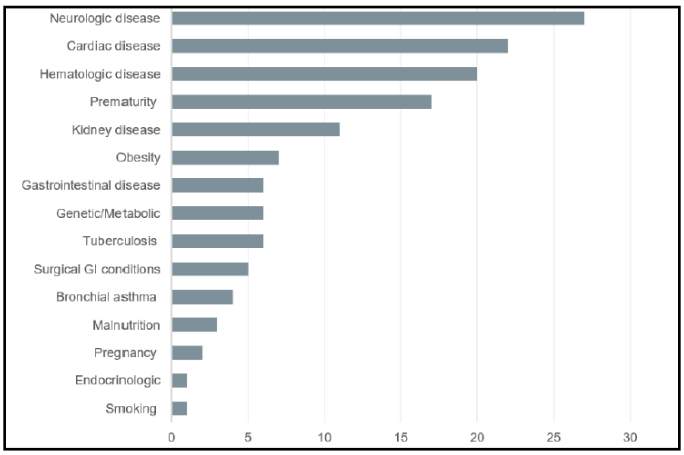

Figure 1. Comorbidities of pediatric COVID-19 non-survivors

DISCUSSION

We describe the first large-scale cohort study of Filipino children with COVID-19 consisting of 2,127 patients reported to the SALVACION registry, a web-based disease surveillance system for COVID-19 in children in the Philippines.

In this study, majority of cases were between 1 to 5 years old with a median age of 5 years, similar to those reported by Nachega, *et al.* in a cohort of sub-Saharan African children and in those reported by Lu, *et al.* among children in Wuhan.[11-12]

This was lower than the median age of 11.9 years reported by Martin, *et al.* in the US.[13] A slight male predominance at 57% was observed in our study, similar to previous reports.[11,12]

Mild and moderate diseases were noted in majority of cases, while severe and critical diseases comprised 15.2% of cases, comparable to the report of Martin, *et al.* where 13.9% met the criteria for severe disease.[13] This was lower than the 47.5% reported by Nachega.[11] The rate of asymptomatic infection was 17.1%, lower than that reported by Chen, *et al.* (32.1%) and Lu, *et al.* (26.4%), which may be attributed to underreporting of asymptomatic cases or lack of testing of asymptomatic children due to inaccessibility, cost or prioritization of symptomatic household members for testing.[12,14] MIS-C cases represent 0.7% of reports, consistent with the study of Dufort, *et al.* (0.6%).[15] MIS-C was most commonly reported in children 6 to 10 years old with a median age of 8 years, consistent with reports of Hoste, *et al.*, Radia, *et al.* and Sharma, *et al.*[16-18]

Tsankov, *et al.* reported that children with comorbidities are 1.79 times more likely to develop severe COVID-19 and/or be admitted to the PICU and 2.8 times more likely to die.[19] In our study, the most common comorbidities in children with severe and critical COVID-19 and among those who died were neurologic disease, hematologic-oncologic disease and cardiac disease. Neurologic disease was also reported by Martin, *et al.*, but concluded that neurologic comorbidities were not significant predictors of severe disease, contrary to our findings.[13] A systematic review by Schlage, *et al.* on COVID-19 and pediatric cancer reported that COVID-19 infection in pediatric cancer patients resulted in severe disease in only a minority of patients; however, despite a milder course, mortality rate was higher than in children with no comorbidities, with deaths attributable to either COVID-19 complications or cancer progression.[20]

In another study by Williams, *et al.*, cardiac comorbidities were most common in children with severe and critical COVID-19.[21]

Among MIS-C cases, obesity was the most common comorbidity, consistent with the report of Hoste, *et al.*[16] With obesity being associated with a chronic subclinical inflammatory status, it is hypothesized that COVID-19 infection triggers a greater hyperinflammatory response and higher endothelial, macrophage and adipocyte activation, leading to considerably elevated inflammatory markers and more severe complications.[22,23]

Fever, cough, and colds were the predominant symptoms. However, gastrointestinal symptoms were also commonly reported, similar to those of Lu, *et al.*[12] Inflammatory markers (CRP, procalcitonin and D-dimer) and markers for organ dysfunction (AST, ALT and LDH) were significantly higher in severe and critical disease compared to non-severe disease, similar to the study of Martin, *et al.*[13] Radiographic findings were mostly normal, as reported in other studies.[24] However, Serrano, *et al.* noted bilateral diffuse peribronchial cuffing as the most common finding, followed by diffuse ground glass opacities.[25]

In the study by Mohammadi, *et al.*, two-thirds of patients have abnormal chest CT scan results, with consolidation and ground-glass opacities.[26] This was lower in our study at only 48.7%, but ground-glass opacities were also the most common finding.

Systemic corticosteroids were the most commonly used immunomodulatory agent in our study with 11% of patients receiving this medication. Among those given systemic corticosteroids, 53.1% had severe/critical COVID-19. About 75% of MIS-C patients were also treated with systemic corticosteroids. This is consistent with the Philippine COVID-19 living recommendations and the PIDSP guidelines, which support the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19.[27,28]

Remdesivir was the most commonly used antiviral agent, given to 14.2% of severe/critical COVID-19 patients, while intravenous immunoglobulin was given to 93.75% of patients diagnosed with MIS-C, following local recommendations.[28]

Our findings showed a high prevalence of antibiotic use, with 58% of patients receiving at least one type of antibiotic. Antibiotic use in children with COVID-19 has been reported to range from 24.5% in a cohort in Latin America to 64% in a cohort in the UK.[29,30] Increased use of antibiotics was seen in children with fever, in those who were hospitalized, had ARDS or abnormal chest x-ray findings, required intensive care, oxygen support (non-invasive or invasive ventilation) and diagnosed with MIS-C with or without cardiac involvement.[29] In our study, antibiotic use was higher in those with severe and critical COVID-19 and MIS-C, likely because symptoms and laboratory findings of these conditions overlap with sepsis; hence, differentiation may be difficult without the benefit of culture results. The increased use of antibiotics during the pandemic has raised the alarm globally on its effect on antimicrobial resistance rates, and antimicrobial stewardship strategies must be incorporated into the management of all children with COVID-19.[31]

The case fatality rate (CFR) in our cohort was 8.6%, higher than that reported by the Philippine's Department of Health among pediatric cases (0.3%), as well as by Kitano, *et al.* in a study of pediatric COVID-19 fatalities in high-income (HIC) and low- and middle-income countries (LMIC).[32] The global estimated pediatric CFR was 0.061%, with LMICs having a significantly higher CFR (0.29%) than HIC (0.03%). Our CFR may be overestimated, as most of the cases reported were hospitalized patients (89%) with comorbidities, predisposing them to severe and critical disease and a higher risk for mortality.

This study has several limitations. The SALVACION registry is used for passive surveillance of cases reported voluntarily by physicians handling pediatric COVID-19. Cases are grossly underreported, as our database only represents 0.6% of the total number of pediatric COVID-19 cases based on the Department of Health's COVID-19 tracker. In addition, almost 50% of reports came from tertiary hospitals and COVID-19 referral centers in the National Capital Region; hence, data may not reflect the overall epidemiology of pediatric COVID-19 in the country. Second, since most reported cases are hospitalized children and children with comorbidities, findings such as disease severity, presence of underlying conditions, use of immunomodulatory treatment options and case-fatality rates may be overestimated and must be interpreted with caution. Third, since data is submitted voluntarily and aggregated from different health facilities, some data may be unavailable or unreported. There may also be limited access to laboratory tests and diagnostic procedures in some regions and laboratory results may not be standardized due to different laboratory analytical techniques and processes.

The SALVACION registry continues to accept reports and data collection is still ongoing. At present, the registry has provided data to national health authorities and specialty medical societies to guide policy decisions on pediatric vaccination and create clinical guidelines and resources on the care for children with COVID-19. Data from the registry also stimulate research and help identify gaps in knowledge for further investigation.

CONCLUSION

Pediatric COVID-19 cases reported to the SALVACION registry are generally mild to moderate in severity. Among severe and critical cases, the most common comorbidities are neurologic, hematologic-oncologic and cardiac diseases. Most patients recovered with supportive management.

High antibiotic usage was seen, which warrants emphasis on judicious antimicrobial use in this cohort.

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