Factors Associated with Adverse Outcomes among SARS-CoV-2 Positive Children in a Tertiary Government COVID-19 Referral Hospital in the Philippines

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ABSTRACT

Background and Objective. Pediatric COVID-19 epidemiology and factors associated with adverse outcomes – *mortality, need for invasive mechanical ventilation, and ICU admission*, are largely unstudied. We described the clinico-demographic characteristics of Filipino pediatric COVID-19 patients and determined the factors associated with adverse outcomes.

Methods. This is a retrospective cohort study of 180 hospitalized SARS-CoV-2-confirmed cases 0-18 years old from April 2020 to August 2021 in a tertiary COVID-19 referral hospital in Manila, National Capital Region. Crude associations were determined using chi-squared or Fisher's exact tests; and medians were compared using the Mann-Whitney test. Factors predictive of mortality were determined using Cox proportional hazards regression analysis. The survivor functions were depicted in graphs.

Results. About 41.67% had mild disease, 58.33% were males, 39.4% aged 0-4 years, and 69.44% had at least one comorbidity. About 9.44% died (adjusted 9.2 persons per 1000 patient-days, 95% CI 5.5%-15.2%), 17.78% needed invasive mechanical ventilation, and 20% needed ICU admission. Independently, severe-critical COVID-19 (HRc 11.51, 95% CI 3.23, 41.06), retractions (HRc 10.30, 95% CI 3.27, 32.47), alar flaring (HRc 4.39, 95% CI 1.53, 12.58), cyanosis (HRc 4.39, 95% CI 1.72, 14.11), difficulty of breathing (HRc 7.99, 95% CI 2.25, 28.71), poor suck/appetite (HRc 4.46, 95% CI 1.59, 12.40), ferritin (HRc 1.01, 95% CI 1.00, 1.01), IL-6 (HRc 1.01, 95% CI 1.00, 1.01), aPTT (HRc 1.05, 95% CI 1.01, 1.10), IVIg (HRc 4.00, 95% CI 1.07, 14.92) and corticosteroid (HRc 6.01, 95% CI 2.04, 17.67) were significant hazards for mortality. In adjusted Cox analysis, only retractions (HRa 34.96, 95% CI 3.36, 363.79), seizure (HRa 9.98, 95% CI 1.76, 56.55), and corticosteroids (HRa 8.21, 95% CI 1.12, 60.38) were significantly associated with mortality while alar flaring appeared to be protective (HRa 0.10, 95% CI 0.01, 0.95). Several clinical characteristics were consistently associated with adverse outcomes.

Conclusions. Majority of hospitalized pediatric COVID-19 patients were very young, males, had mild disease, and had at least one comorbidity. Mortality, invasive mechanical ventilation, and ICU admission were relatively low. Except for alar flaring which appeared to be protective, retractions, seizure, and use of corticosteroids were associated with adverse outcomes.

Keywords: COVID-19, epidemiology, hazards, Philippines, children, pediatrics

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INTRODUCTION

COVID-19 disease is caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a Betacoronavirus most closely related to the Chinese horseshoe bat SARS coronavirus.[1] The outbreak started in Wuhan, Hubei, China in December 2019. It was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 and as of April 17, 2022, the total number of COVID-19 cases globally is 500.18 million with a recorded 6.19 million deaths.[2] Early in the pandemic, few cases of children were reported but retrospectively, data shows that children were not spared from being infected.[3-5] COVID-19 mostly affects the adult population and data about its impact on the pediatric population are still evolving.

COVID-19 infection in children is thought to be milder in severity due to a more active innate immunity, particularly because of childhood vaccine exposure.[6] A clinical analysis of 25 COVID-19 pediatric patients in China showed that the median age was 11 years, 32% of the subjects were asymptomatic, and 16% were tagged as very mild cases with most common symptoms being cough and fever.[7] Analysis of 2,135 pediatric COVID patients reported to the Chinese Center for Disease Control (CDC) showed that 2,008 patients or 94.1% of all cases were asymptomatic to moderate.[8] Children are less likely to be tested for COVID-19 due to less severe symptomatology hence, hospital admission rate and SARS-CoV-2 testing rate tend to underestimate the true burden of disease.[3,9,10] The above data have made children a minority in terms of the total number of infections worldwide; however, the trends are continually evolving.

Globally, as of June 2022, among the 4.4 million COVID-19-related mortalities, more than 17,200 (0.4%) occurred in children and adolescents under 20 years of age.[11] Majority of these deaths occurred among adolescents 10-19 years old.[11] A systematic review involving 7780 pediatric COVID-19 patients revealed a mortality rate of 0.1% with only 1% of the cases being severe.[12] This review mostly involved studies from China with few accounts from Japan, Korea, Malaysia, and Singapore. Children and young people maintained a low rate of COVID-19-related mortality, but they were not spared from collateral damage to their health and safety.[13,14]

There are few studies done about the risk factors for mortality and other adverse events among pediatric COVID-19 patients. A nationwide study in Brazil showed an association of COVID-19-related death with age, indigenous ethnicity, poor geopolitical region, and existing comorbidities.[15] One fatality study on COVID-19 showed that older age, comorbidities, gender, smoking status, obesity, age, acute kidney injury, and D-dimer levels are associated factors for mortality from coronavirus.[16] In another study, factors associated with mortality included cardiac or pulmonary comorbidities, admission hypoxemia, and lower respiratory symptoms.[17] There is scarcity of data about factors leading to Pediatric ICU (PICU) admissions and invasive mechanical ventilation among pediatric COVID-19 patients from low-middle-income countries (LMICs) and studies generally focus on multisystem inflammatory syndrome in children (MIS-C).[17-20]

There is little information about the epidemiology of pediatric COVID-19 in the Asian region, particularly in the LMICs, and the South and Southeast Asian (SEA) regions. During the period when Alpha and Delta COVID-19 variants were dominant in Thailand, 2.3% of 698 pediatric COVID cases were severe and critical, with a mortality rate of only 0.1%.[21] At the time of this writing, there has been no published study in the Philippines about pediatric COVID-19 patients' clinico-demographic characteristics and their association with adverse events, including mortality.[22] To date, there is no study done in the Philippines analyzing the hazards of adverse outcomes (mortality, need for mechanical ventilation, and need for ICU admission) in relation to the clinico-demographic profile of pediatric COVID-19 patients. This study looks at the characteristics of pediatric COVID-19 patients admitted in a tertiary government COVID-19 referral center and their hazards to adverse outcomes, especially mortality.

MATERIALS AND METHODS

Study design

This was a single-center retrospective cohort study of pediatric patients in the Philippine General Hospital (PGH) with confirmed COVID-19 disease. The exposure variables used were demographic characteristics age and sex, clinical characteristics (i.e., COVID-19 severity, presenting signs and symptoms on admission, anthropometrics, and comorbidities), diagnostic tests on admission (i.e., laboratory tests and imaging), and therapeutic regimen received during the course of admission of the patients.

Setting

The Philippine General Hospital is a tertiary government hospital in the capital city, Manila, and was designated as one of three COVID-19 referral centers in the Philippines since March 30, 2020 by the Department of Health.[22] The PGH is the largest tertiary hospital in the Philippines and is run by its state university, the University of the Philippines. From April 1, 2020 to August 31, 2021, a total of 214 pediatric patients were treated for COVID-19 in PGH as reported to the passive reporting system of the Pediatric Infectious Disease Society of the Philippines, Inc (PIDSP), the SALVACION (Surveillance and Analysis of COVID-19 in Children Nationwide) Registry.

Study Subjects

Included in this study was a dynamic cohort of PGH pediatric patients treated for COVID-19 from the PIDSP records. The inclusion criteria included Filipino patients, 0-18 years old, SARS-CoV-2 positive via RT-PCR, admitted at

the PGH within the period of April 1, 2020 to August 31, 2021. Patients who were classified as COVID-19 suspects or probable cases with unknown RT-PCR results were excluded in the study.

Sampling

In order to test the hypothesis that the hazard of mortality is two times higher among pediatric patients with severe to critical COVID-19 as compared to those with asymptomatic to moderate disease, assuming an alpha error probability of 0.05, power of 80%, an event probability of 50%, and a squared correlation of 10%, a minimum of 146 patients were needed in the study. The *power cox* command in STATA 16 (StataCorp, Texas, USA) was used to estimate the minimum sample size requirement for this study.

Data Collection and Organization

The pieces of data on pediatric COVID-19 patients admitted in PGH were requested from the PIDSP registry managers. Upon approval, an anonymized Excel file was forwarded to the investigators via email. The clinico-demographic variables and outcomes of the patients were abstracted from the file by the two investigators (MDCM and ARM). All variables were thoroughly checked for completeness, accuracy, and consistency prior to analysis. Recoding of categorical data was done as appropriate.

The COVID-19 disease severity was operationally defined using the World Health Organization's COVID-19 Clinical management living guidance and the Pediatric Infectious Disease Society of the Philippines, Inc.'s (PIDSP) interim guidelines on the screening, classification, and management of pediatric patients with suspected or confirmed coronavirus disease 2019. Mild disease was defined as symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. Moderate disease was defined as with clinical signs of non-severe pneumonia and no signs of severe pneumonia. Severe COVID-19 was having clinical signs of pneumonia with at least one of the following signs: central cyanosis, peripheral O2 saturation of <95%, OR tachypnea. Critical COVID-19 was defined as having respiratory failure, septic shock, and/or multiple organ dysfunction.

The patients' demographic characteristics included age and sex while the clinical characteristics included COVID-19 severity, signs, symptoms, anthropometrics, comorbidities, diagnostic tests, and therapeutic interventions received. Obesity was considered separately from other endocrinologic comorbidities. Hematologic and oncologic disorders were counted as one disease entity. Tuberculosis pertained to *Mycobacterium tuberculosis* infection in any site. The diagnostic tests included complete blood count (CBC), arterial blood gas (ABG), coagulation parameters, transaminases, and inflammatory markers. Abnormal chest radiograph and computed tomography (CT) were defined as findings consistent with pneumonia. Investigational drugs pertained to oseltamivir, remdesivir, tocilizumab, and enoxaparin. Other antimicrobials pertained to antibiotics administered for co-existing disease entities and independent of the treatment for COVID-19. These included cefuroxime, ceftriaxone, amikacin, colistin, ampicillin-sulbactam, second-line anti-TB medications, metronidazole, clindamycin, ceftazidime, levofloxacin, ciprofloxacin, penicillin G, vancomycin, penicillin VK, and co-amoxiclav. Nutritional supplements used as adjunct for COVID-19 management included Zinc and Vitamin D3 (cholecalciferol).

The clinical outcomes were mortality dichotomized into dead or alive; need for mechanical ventilation dichotomized into 1) No oxygen support/with non-invasive oxygen support, i.e., nasal cannula, face mask, nasal continuous positive airway pressure (nCPAP) and 2) invasive mechanical ventilation or those warranting intubation; and need for intensive care unit (ICU) admission which was dichotomized into 1) Ward admission only and 2) ICU admission.

Statistical Analyses

A dataset from Excel was imported into STATA 14 (StataCorp, Texas, USA) for analysis. A total of 214 unique observations were noted in the dataset but only 180 observations were included in the analysis (excluded were 32 COVID-19 negative patients by RT-PCR and two patients with unknown mortality outcome). Categorical data were summarized in terms of frequencies and percentages, and were compared using Fisher's exact test or Pearson's chi-squared test, as appropriate. The former was used when more than 20% of the cells had an expected value of less than or equal to five or if any of the cells had an observed value of zero. Skewed continuous data were summarized using medians (p25, p75) and were compared using Mann-Whitney test. The median survival time was estimated along with the adjusted mortality rate per 1000 patient-days contribution. Both the crude and adjusted hazard ratios for mortality were estimated using Cox proportional hazards regression analysis, which is the appropriate technique for analyzing data with censored outcomes. The Cox proportional hazard assumption was tested using Schoenfeld Residuals following Cox regression (i.e., p-value >0.05 assumes that the PH assumption holds). The variables included in the adjusted model were the pre-identified age group, sex, COVID-19 severity on admission, presence/absence of comorbidity, and COVID-19 signs and symptoms and therapeutics with p-values less than 0.10. The adjusted survivor functions were presented in graphs. The hazards for need for mechanical ventilation and need for ICU admission were planned initially in the protocol. However, the dataset obtained did not contain time data when mechanical ventilation was initiated or when the patients were admitted in the ICU. Furthermore, in the adjusted hazards analysis, the diagnostic tests were not included due to insufficient number of patients who underwent the laboratory tests at baseline. A p-value of less than 0.05 was considered significant for all tests.

Ethical Considerations

The study has been approved by the University of the Philippines Manila Research Ethics Board and the Philippine General Hospital Expanded Hospital Research Office. This study strictly adhered to the provisions of the Philippine Data Privacy Act of 2012, the guidelines set by the Philippine National Ethical Guidelines for Health and Health-related Research (2017), and the principles of good clinical and research practices in medicine.

RESULTS

A total of 180 unique observations were eligible for analysis. Table 1 shows that most of the patients were in the 0-4 age group (39.4%) and the majority were males (58.33%). The majority of the patients had at least one comorbidity (69.44%). Most patients had mild disease (41.67%). Majority of the asymptomatic patients were at least 10 years old (56.5%) while the majority of the mild, moderate-severe, and critical COVID are in the 0-9 age group.

Association of Patient Characteristics and COVID-19 Severity

COVID-19 severity, categorized into asymptomatic, mild, moderate-severe, and critical, was not significantly associated with sex (p = 0.270) and age group (p=0.094). Similarly, COVID-19 severity was not significantly associated with the following comorbidities: obesity, bronchial asthma, tuberculosis, cardiac disease, renal, neurologic (i.e., epilepsy), prematurity, endocrinologic, rheumatologic, immunologic, dengue, healthcare-associated pneumonia, and sepsis (all p-values greater than 0.05). However, hematologic-oncologic (i.e., acute lymphoblastic leukemia), gastrointestinal (i.e., appendicitis and malnutrition), and genetic/metabolic diseases were significantly associated with COVID-19 severity (Table 1).

Presenting Signs and Symptoms

The symptoms and signs of children with COVID-19 are presented in Table 2. Of the 180 patients, the three most common signs were fever (42.22%), rales/crackles/rhonchi (20.56%), and retractions (17.22%) while the most common symptoms were cough (27.22%), difficulty of breathing (23.33%), and vomiting (19.44%). Cyanosis, wheezing, watery stools, seizure, muscle pain, sore throat, anosmia and

Table 1. Patient Characteristics by Level of COVID-19 Severity

Characteristics	COVID-19 severity				
	Asymptomatic (n=46)	Mild (n=75)	Moderate to severe (n=45)	Critical (n=14)	*p*-value
Sex					
Female	15 (32.61)	36 (48.00)	20 (44.44)	4 (28.57)	0.270[b]
Male	31 (67.39)	39 (52.00)	25 (55.56)	10 (71.43)	
Age group					
0-4	14 (30.43)	26 (34.67)	22 (48.89)	9 (64.29)	0.094[a]
5-9	6 (13.04)	15 (20.00)	5 (11.11)	4 (28.57)	
10-14	15 (32.61)	16 (21.33)	9 (20.00)	1 (7.14)	
15-18	11 (23.91)	18 (24.00)	9 (20.00)	0 (0.00)	
Comorbidities					
With comorbid	25 (20.00)	55 (44.00)	34 (27.20)	11 (8.80)	0.078[b]
Obese	1 (2.17)	0 (0.00)	3 (6.67)	0 (0.00)	0.094[a]
Bronchial asthma	0 (0.00)	0 (0.00)	2 (4.44)	0 (0.00)	0.146[a]
Tuberculosis	3 (6.52)	6 (8.00)	3 (6.67)	1 (7.14)	1.000[a]
Cardiac disease	4 (8.70)	7 (9.33)	8 (17.78)	2 (14.29)	0.473[b]
Hematologic / Oncologic	2 (4.35)	20 (26.67)	4 (8.89)	1 (7.14)	**0.003[b]**
Renal	1 (2.17)	3 (4.00)	4 (8.89)	0 (0.00)	0.443[a]
Neurologic	8 (17.39)	6 (8.00)	10 (22.22)	3 (21.43)	0.146[b]
Prematurity	0 (0.00)	1 (1.33)	1 (2.22)	0 (0.00)	0.786[a]
Gastrointestinal	7 (15.22)	17 (22.67)	2 (4.44)	1 (7.14)	**0.045[a]**
Genetic / Metabolic	0 (0.00)	0 (0.00)	2 (4.44)	1 (7.14)	**0.031[a]**
Endocrinologic	0 (0.00)	1 (1.33)	1 (2.22)	0 (0.00)	0.786[a]
Rheumatologic	1 (2.17)	2 (2.67)	0 (0.00)	0 (0.00)	0.838[a]
Immunologic	0 (0.00)	1 (1.33)	0 (0.00)	0 (0.00)	1.000[a]
Dengue fever	0 (0.00)	1 (1.33)	1 (2.22)	0 (0.00)	0.786[a]
Healthcare-associated pneumonia	1 (2.17)	4 (5.33)	1 (2.22)	2 (14.29)	0.244[a]
Sepsis	1 (2.17)	3 (4.00)	2 (4.44)	1 (7.14)	0.708[a]

[a] *Fisher's exact test*, [b] *Pearson's chi-squared test*

Table 2. Presenting Signs and Symptoms among COVID-19 Pediatric Patients in the Philippine General Hospital

Signs and symptoms	Frequency (%) n=180
Signs	
Fever	76 (42.22)
Rales/Crackles/Rhonchi	37 (20.56)
Retractions	31 (17.22)
Signs of dehydration	21 (11.67)
Alar flaring	18 (10.00)
Cyanosis	16 (8.89)
Wheezing	7 (3.89)
Symptoms	
Cough	49 (27.22)
Difficulty of breathing	42 (23.33)
Vomiting	35 (19.44)
Poor suck / appetite	33 (18.33)
Abdominal pain	29 (16.11)
Colds	19 (10.56)
Watery stools	14 (7.78)
Seizure	11 (6.11)
Muscle pain	3 (1.67)
Sore throat	2 (1.11)
Anosmia	1 (0.56)
Ageusia	1 (0.56)

ageusia were the least common signs and symptoms (i.e., less than 10%).

Association of Patient Characteristics and Mortality

The association of clinico-demographic characteristics and mortality using univariate analysis are presented in Table 3. Majority of the patients, 163 (90.56%), were survivors while only 17 (9.44%) were non-survivors. Age and sex were not significantly associated with mortality, p-values 0.290 and 0.636, respectively. COVID-19 severity was associated with mortality with the majority of non-survivors (76.47%) having severe or critical COVID-19 disease, p <0.001. In addition, the presence of retractions, alar flaring, cyanosis, difficulty of breathing, and poor suck/appetite were significantly associated with mortality (all p-values ≤0.001). The median weight of non-survivors, 13 kg, was significantly different from survivors, 22 kg (p = 0.0165) but not height (p = 0.0714). Among the comorbidities, only tuberculosis and healthcare-associated pneumonia were significantly associated with mortality, p-values 0.023 and 0.029, respectively. The results of complete blood count, arterial blood gas, CRP, ESR, procalcitonin, transaminases, LDH, and creatine kinase were not significantly different between survivors and non-survivors (p>0.05). However, the coagulation parameters such as D-dimer, ferritin, IL-6, protime, INR, and aPTT were found to be significantly different between survivors and non-survivors. The proportions of patients with abnormal chest imaging findings were not significantly different between survivors and non-survivors. Furthermore, the proportions of patients who received the investigational drugs oseltamivir, remdesivir, tocilizumab, and enoxaparin were not significantly different between the two outcome groups. None of the patients ever received chloroquine, hydroxychloroquine, interferon, lopinavir, nor ritonavir. The proportion of patients who received azithromycin (p = 0.004), IVIg (p = 0.008) as well as corticosteroids (p <0.001) was significantly higher in the non-survivor group. The proportion of patients who received other antimicrobials, vitamin D3 or zinc were not significantly different between survivors and non-survivors.

Association of Patient Characteristics and Need for Invasive Mechanical Ventilation

Table 4 summarizes the univariate association of clinico-demographic characteristics and the need for invasive oxygen support. A total of 32 patients (17.78%) received mechanical ventilation support while 148 patients (82.22%) received none (i.e., room air), non-invasive oxygen support such as nasal/oronasal continuous positive airway pressure (CPAP). Age, but not sex, was significantly associated with mechanical ventilation with the majority of mechanically ventilated patients belonging to the 0-4 age group (59.38%), p = 0.039. COVID-19 severity was also associated with mechanical ventilation with more than 55% of the mechanically ventilated patients having severe or critical disease, p <0.001. Similarly, patients who presented with respiratory distress signs including rales/crackles/rhonchi, retractions, alar flaring, cyanosis, wheezing and respiratory distress symptoms such as difficulty of breathing and cough were all significantly associated with mechanical ventilation, p-value range <0.001 to 0.021. Patients who had signs of dehydration, poor suck/appetite, abdominal pain, or seizure were significantly associated with mechanical ventilation. Other signs and symptoms such as fever, vomiting, colds, watery stools, muscle pain, sore throat, anosmia, and ageusia were not significantly associated with invasive ventilatory support, all p-values >0.05. There was a statistically significant difference between the median height and weight of patients who were mechanically ventilated and those who were not. Specifically, patients who had ventilatory support were shorter (85 cm versus 132 cm) and lighter (10 kg versus 25.5 kg), p = 0.0006 and 0.0010, respectively. Except for healthcare-associated pneumonia (p = 0.035), none of the comorbidities were significantly associated with mechanical ventilation. Furthermore, there was no significant difference in the median results of most laboratory tests except for INR and aPTT which are higher in the mechanically ventilated patients, 1.37 vs 1.12 (p = 0.0454) and 38.05 vs 29.0 (p = 0.0044), respectively. The proportion of patients with abnormal chest x-ray findings was also significantly higher among mechanically ventilated patients, 80.65% versus 52.34%, p = 0.004. There was no significant difference in the proportion of patients with abnormal chest CT scan results between the non-invasive and invasive oxygen support groups. Likewise, the proportion of patients who received the investigational drugs were not

Table 3. Association of Patient Characteristics and Need for Mortality

Clinico-demographic profile	Mortality			
	Total (n= 180)	Survivor (n= 163)	Non-survivor (n=17)	*p*-value
Demographic characteristics				
Age				
0-4	71 (39.44)	62 (38.04)	9 (52.94)	0.290[a]
5-9	30 (16.67)	26 (15.95)	4 (23.53)	
10-14	41 (22.78)	38 (23.31)	3 (17.65)	
15-18	38 (21.11)	37 (22.70)	1 (5.88)	
Sex				
Male	105 (58.33)	96 (58.90)	9 (52.94)	0.636[b]
Female	75 (41.67)	67 (41.10)	8 (47.06)	
Clinical characteristics				
COVID-19 Severity				
Asymptomatic	46 (25.56)	46 (28.22)	0 (0.00)	**<0.001[a]**
Mild	75 (41.67)	71 (43.56)	4 (23.53)	
Moderate	28 (15.56)	28 (17.18)	0 (0.00)	
Severe	17 (9.44)	14 (8.59)	3 (17.65)	
Critical	14 (7.78)	4 (2.45)	10 (58.82)	
Signs				
Fever	76 (42.22)	67 (41.10)	9 (52.94)	0.347[b]
Rales/Crackles/Rhonchi	37 (20.56)	29 (17.79)	8 (47.06)	**0.009[a]**
Retractions	31 (17.22)	19 (11.66)	12 (70.59)	**<0.001[a]**
Signs of dehydration	21 (11.67)	17 (10.43)	4 (23.53)	0.118[a]
Alar flaring	18 (10.00)	11 (6.75)	7 (41.18)	**<0.001[a]**
Cyanosis	16 (8.89)	9 (5.52)	7 (41.18)	**<0.001[a]**
Wheezing	7 (3.89)	5 (3.07)	2 (11.76)	0.133[a]
Symptoms				
Cough	49 (27.22)	40 (24.54)	9 (52.94)	**0.020[a]**
Difficulty of breathing	42 (23.33)	29 (17.79)	13 (76.47)	**<0.001[a]**
Vomiting	35 (19.44)	34 (20.86)	1 (5.88)	0.201[a]
Poor suck / appetite	33 (18.33)	24 (14.72)	9 (52.94)	**0.001[a]**
Abdominal pain	29 (16.11)	29 (17.79)	0 (0.00)	0.079[a]
Colds	19 (10.56)	19 (11.66)	0 (0.00)	0.223[a]
Watery stools	14 (7.78)	12 (7.36)	2 (11.76)	0.626[a]
Seizure	11 (6.11)	8 (4.91)	3 (17.65)	0.072[a]
Muscle pain	3 (1.67)	3 (1.84)	0 (0.00)	1.000[a]
Sore throat	2 (1.11)	1 (0.61)	1 (5.88)	0.180[a]
Anosmia	1 (0.56)	1 (0.61)	0 (0.00)	1.000[a]
Ageusia	1 (0.56)	1 (0.61)	0 (0.00)	1.000[a]
Anthropometrics				
Height, cm	121 (82, 150)	126 (82.5, 150.5)	93 (64, 120)	0.0714[c]
Weight, kg	20.8 (9, 41.6)	22 (10.2, 43.1)	13 (5.55, 23.2)	0.0165[c]
Comorbidities				
Obese	4 (2.22)	4 (2.45)	0 (0.00)	1.000[a]
Bronchial Asthma	2 (1.11)	2 (1.23)	0 (0.00)	1.000[a]
Tuberculosis	13 (7.22)	9 (5.52)	4 (23.53)	**0.023[a]**
Cardiac	21 (11.67)	18 (11.04)	3 (17.65)	0.425[a]
Hematologic / Oncologic	27 (15.00)	24 (14.72)	3 (17.65)	0.724[a]
Renal	8 (4.44)	8 (4.91)	0 (0.00)	1.000[a]
Neurologic	27 (15.00)	26 (15.95)	1 (5.88)	0.475[a]
Prematurity	2 (1.11)	2 (1.23)	0 (0.00)	1.000[a]
Gastrointestinal	27 (15.00)	26 (15.95)	1 (5.88)	0.475[a]
Genetic / Metabolic	3 (1.67)	2 (1.23)	1 (5.88)	0.259[a]
Endocrinologic	2 (1.11)	2 (1.23)	0 (0.00)	1.000[a]
Rheumatologic	3 (1.67)	3 (1.84)	0 (0.00)	1.000[a]
Immunologic	1 (0.56)	1 (0.61)	0 (0.00)	1.000[a]
Dengue Fever	2 (1.11)	2 (1.23)	0 (0.00)	1.000[a]
Healthcare-associated pneumonia	8 (4.44)	5 (3.07)	3 (17.65)	**0.029[a]**
Sepsis	7 (3.89)	5 (3.07)	2 (11.76)	0.133[a]

Table 3. Association of Patient Characteristics and Need for Mortality *(continued)*

Clinico-demographic profile	Mortality			
	Total (n= 180)	Survivor (n= 163)	Non-survivor (n=17)	*p*-value
Diagnostics				
CBC				
Hemoglobin	116 (39, 132)	115 (27, 132)	122 (99, 135)	0.2170[c]
Hematocrit	0.37 (0.33, 0.42)	0.37 (0.33, 0.42)	0.38 (0.34, 0.40)	0.7335[c]
White blood cells	11.5 (8, 15.8)	11.5 (7.9, 15.8)	13.1 (9.3, 15.1)	0.8148[c]
Neutrophils	0.67 (0.52, 0.81)	0.67 (0.51, 0.81)	0.66 (0.60, 0.81))	0.3751[c]
Lymphocytes	0.24 (0.11, 0.38)	0.24 (0.12, 0.38)	0.26 (0.09, 0.33)	0.7643[c]
Platelets	328 (231, 417)	329 (242, 417)	265 (160, 407)	0.2039[c]
ABG				
pH	7.41 (7.32, 7.45)	7.42 (7.34, 7.46)	7.39 (7.24, 7.42)	0.2655[c]
$PaCO_2$	30 (24, 39)	30.5 (25.5, 39.5)	28 (17, 33)	0.3118[c]
HCO_3	20.3 (14, 23.5)	20.45 (16.85, 23.8)	18.8 (12.6, 21.2)	0.3026[c]
PaO_2	110 (73, 167)	109 (71.5, 159)	118 (91, 167)	0.6133[c]
Other tests				
D-dimer	2.83 (1.01, 4.23)	1.79 (0.97, 3.39)	4.8 (3.32, 10.57)	**0.0017**[c]
Ferritin	226.5 (82.6, 686)	165 (82.3, 339)	1540 (657.6, 3415)	**0.0039**[c]
CRP	22.63 (6, 96)	24 (6, 96)	9 (6, 85)	0.4741[c]
ESR	52 (11, 76)	50 (7.67, 76.5)	71 (71, 71)	0.5930[c]
Procalcitonin	0.28 (0.09, 2.93)	0.23 (0.09, 2.56)	1.01 (0.15, 35.65)	0.0877[c]
AST	64 (38, 117)	49 (34, 85)	106.5 (64, 188)	0.0600[c]
ALT	35 (20, 93)	28 (18, 93)	44 (28, 68)	0.3149[c]
LDH	451.5 (329, 897)	446 (316, 679)	982 (348, 1455)	0.0590[c]
Creatine Kinase	94 (44, 653)	113.5 (48, 1399.5)	68 (44, 380)	0.4386[c]
IL-6	94.5 (26.5, 389)	84 (20, 221)	1008 (71, 2337)	**0.0480**[c]
PT	14.8 (13.2, 22.3)	13.7 (12.9, 15)	23.7 (16.4, 46.2)	**0.0043**[c]
INR	1.2 (1.05, 1.43)	1.1 (1.03, 1.23)	1.48 (1.32, 1.88)	**0.0031**[c]
aPTT	30.9 (26.8, 35.7)	28.5 (26.6, 32.7)	41.15 (34.8, 48.4)	**0.0010**[c]
Imaging				
Chest x-ray, abnormal	92 (57.86)	79 (55.63)	13 (76.47)	0.123[a]
Chest CT scan, abnormal	28 (100.00)	23 (100.00)	5 (100.00)	-
Therapeutics				
Investigational Drugs				
Remdesivir	8 (4.44)	7 (4.29)	1 (5.88)	0.555[a]
Tocilizumab	2 (1.11)	1 (0.61)	1 (5.88)	0.180[a]
Enoxaparin	1 (0.56)	0 (0.00)	1 (5.88)	0.094[a]
Antimicrobials				
Azithromycin	19 (10.56)	13 (7.98)	6 (35.29)	**0.004**[a]
Other antimicrobials	110 (61.11)	96 (58.90)	14 (82.35)	0.059[b]
Intravenous immunoglobulin (IV Ig)	10 (5.56)	6 (3.68)	4 (23.53)	**0.008**[a]
Corticosteroids	34 (18.89)	23 (14.11)	11 (64.71)	**<0.001**[a]
Nutritional Supplements				
Zinc	129 (71.67)	120 (73.62)	9 (52.94)	0.090[a]
Vitamin D3	122 (67.78)	113 (69.33)	9 (52.94)	0.169[b]

[a] *Fisher's exact test*, [b] *Pearson's chi-squared test*, [c] *Mann-Whitney test*

Table 4. Association of Patient Characteristics and Need for Mechanical Ventilation

Clinico-demographic profile	Need for Mechanical Ventilation			
	Total (n= 180)	None / Non-invasive O_2 support / CPAP (n=148)	Invasive Mechanical Ventilation (n=32)	*p*-value
Demographic characteristics				
Age				
0-4	71 (39.44)	52 (35.14)	19 (59.38)	**0.039**[b]
5-9	30 (16.67)	24 (16.22)	6 (18.75)	
10-14	41 (22.78)	37 (25.00)	4 (12.50)	
15-18	38 (21.11)	35 (23.65)	3 (9.38)	
Sex				
Male	105 (58.33)	85 (57.43)	20 (62.50)	0.598[b]
Female	75 (41.67)	63 (42.57)	12 (37.50)	
Clinical characteristics				
COVID-19 Severity				
Asymptomatic	46 (25.56)	41 (27.70)	5 (15.63)	**<0.001**[a]
Mild	75 (41.67)	67 (45.27)	8 (25.00)	
Moderate	28 (15.56)	27 (18.24)	1 (3.13)	
Severe	17 (9.44)	12 (8.11)	5 (15.63)	
Critical	14 (7.78)	1 (0.68)	13 (40.63)	
Signs				
Fever	76 (42.22)	60 (40.54)	16 (50.00)	0.326[b]
Rales/Crackles/Rhonchi	37 (20.56)	23 (15.54)	14 (43.75)	**0.001**[a]
Retractions	31 (17.22)	14 (9.46)	17 (53.13)	**<0.001**[b]
With signs of dehydration	21 (11.67)	10 (6.76)	11 (34.38)	**<0.001**[a]
Alar flaring	18 (10.00)	8 (5.41)	10 (31.25)	**<0.001**[a]
Cyanosis	16 (8.89)	7 (4.73)	9 (28.13)	**<0.001**[a]
Wheezing	7 (3.89)	2 (1.35)	5 (15.63)	**0.002**[a]
Symptoms				
Cough	49 (27.22)	35 (23.65)	14 (43.75)	**0.021**[b]
Difficulty of breathing	42 (23.33)	22 (14.86)	20 (62.50)	**<0.001**[b]
Vomiting	35 (19.44)	31 (20.95)	4 (12.50)	0.274[b]
Poor suck / appetite	33 (18.33)	21 (14.19)	12 (37.50)	**0.002**[b]
Abdominal pain	29 (16.11)	29 (19.59)	0 (0.00)	**0.003**[a]
Colds	19 (10.56)	17 (11.49)	2 (6.25)	0.534[a]
Watery stools	14 (7.78)	11 (7.43)	3 (9.38)	0.717[a]
Seizure	11 (6.11)	6 (4.05)	5 (15.63)	**0.027**[a]
Muscle pain	3 (1.67)	2 (1.35)	1 (3.13)	0.446[a]
Sore throat	2 (1.11)	1 (0.68)	1 (3.13)	0.325[a]
Anosmia	1 (0.56)	1 (0.68)	0 (0.00)	1.000[a]
Ageusia	1 (0.56)	1 (0.68)	0 (0.00)	1.000[a]
Anthropometrics				
Height, cm	121 (82, 150)	132 (87, 152)	85 (64, 113)	0.0006[c]
Weight, kg	20.8 (9, 41.6)	25.5 (12.0, 44.0)	10 (5.3, 17.9)	0.0010[c]
Comorbidities				
Obese	4 (2.22)	4 (2.70)	0 (0.00)	1.000[a]
Bronchial Asthma	2 (1.11)	1 (0.68)	1 (3.13)	0.325[a]
Tuberculosis	13 (7.22)	10 (6.76)	3 (9.38)	0.705[a]
Cardiac	21 (11.67)	16 (10.81)	5 (15.63)	0.542[a]
Hematologic / Oncologic	27 (15.00)	23 (15.54)	4 (12.50)	0.790[a]
Renal	8 (4.44)	8 (5.41)	0 (0.00)	0.354[a]
Neurological	27 (15.00)	20 (13.51)	7 (21.88)	0.273[a]
Prematurity	2 (1.11)	2 (1.35)	0 (0.00)	1.000[a]
Gastrointestinal	27 (15.00)	25 (16.89)	2 (6.25)	0.174[a]
Genetic / Metabolic	3 (1.67)	1 (0.68)	2 (6.25)	0.082[a]
Endocrinologic	2 (1.11)	2 (1.35)	0 (0.00)	1.000[a]
Rheumatologic	3 (1.67)	3 (2.03)	0 (0.00)	1.000[a]
Immunologic	1 (0.56)	1 (0.68)	0 (0.00)	1.000[a]
Dengue Fever	2 (1.11)	2 (1.35)	0 (0.00)	1.000[a]
Healthcare-associated pneumonia	8 (4.44)	4 (2.70)	4 (12.50)	0.035[a]
Sepsis	7 (3.89)	5 (3.38)	2 (6.25)	0.609[a]

Table 4. Association of Patient Characteristics and Need for Mechanical Ventilation *(continued)*

Clinico-demographic profile	Need for Mechanical Ventilation			
	Total (n= 180)	None / Non-invasive O_2 support / CPAP (n=148)	Invasive Mechanical Ventilation (n=32)	*p*-value
Diagnostics				
CBC				
Hemoglobin	116 (39, 132)	115 (38, 131)	121 (67, 137)	0.4808[c]
Hematocrit	0.37 (0.33, 0.42)	0.37 (0.33, 0.42)	0.38 (0.34, 0.44)	0.2846[c]
White blood cells	11.5 (8, 15.8)	11.75 (7.85, 16.6)	11.1 (8.8, 15.1)	0.6114[c]
Neutrophils	0.67 (0.52, 0.81)	0.66 (0.52, 0.81)	0.72 (0.51, 0.81)	0.5855[c]
Lymphocytes	0.24 (0.11, 0.38)	0.24 (0.12, 0.36)	0.26 (0.10, 0.46)	0.5550[c]
Platelets	328 (231, 417)	332 (243, 435)	271 (148, 373)	0.0737[c]
ABG				
pH	7.41 (7.32, 7.45)	7.41 (7.32, 7.44)	7.42 (7.31, 7.48)	0.5549[c]
$PaCO_2$	30 (24, 39)	28 (24.5, 38.5)	31 (20, 40)	0.6850[c]
HCO_3	20.3 (14, 23.5)	19.6 (14.8, 22.4)	20.7 (13.0, 27.9)	0.6319[c]
PaO_2	110 (73, 167)	101.5 (60, 158.5)	118 (92, 168)	0.2852[c]
Other tests				
D-dimer	2.83 (1.01, 4.23)	2.54 (0.97, 4.12)	3.32 (1.39, 4.8)	0.3468[c]
Ferritin	226.5 (82.6, 686)	173 (82.6, 339)	686 (107, 1800)	0.0840[c]
CRP	22.63 (6, 96)	24 (6, 96)	12 (6, 96)	0.6651[c]
ESR	52 (11, 76)	58.5 (7.66, 87)	48 (12, 71)	0.5582[c]
Procalcitonin	0.28 (0.09, 2.93)	0.26 (0.09, 2.71)	0.60 (0.12, 4.35)	0.3176[c]
AST	64 (38, 117)	55 (34, 90)	84 (49, 188)	0.0989[c]
ALT	35 (20, 93)	35 (18, 93)	32 (22, 68)	0.6251[c]
LDH	451.5 (329, 897)	450 (316, 598)	882 (348, 990)	0.1373[c]
Creatine Kinase	94 (44, 653)	82 (41, 1500)	150 (56, 341)	0.9611[c]
IL-6	94.5 (26.5, 389)	105 (24, 271)	85 (29, 1115)	0.7441[c]
PT	14.8 (13.2, 22.3)	14 (13, 15)	17 (14.6, 36.4)	0.0620[c]
INR	1.2 (1.05, 1.43)	1.12 (1.04, 1.23)	1.37 (1.17, 1.85)	**0.0454**[c]
aPTT	30.9 (26.8, 35.7)	29 (26.7, 32)	38.05 (32.3, 43.9)	**0.0044**[c]
Imaging				
Chest x-ray, abnormal	92 (57.86)	67 (52.34)	25 (80.65)	**0.004**[b]
Chest CT scan, abnormal	28 (100.00)	21 (100.00)	7 (100.00)	-
Therapeutics				
Investigational Drugs				
Oseltamivir	180 (100.00)	148 (100.00)	32 (100.00)	-
Remdesivir	8 (4.44)	5 (3.38)	3 (9.38)	0.152[a]
Tocilizumab	2 (1.11)	1 (0.68)	1 (3.13)	0.325[a]
Enoxaparin	1 (0.56)	0 (0.00)	1 (3.13)	0.178[a]
Antimicrobials				
Azithromycin	19 (10.56)	10 (6.76)	9 (28.13)	**0.002**[a]
Other antimicrobials	110 (61.11)	86 (58.11)	24 (75.00)	0.076[b]
IVIG	10 (5.56)	3 (2.03)	7 (21.88)	**<0.001**[a]
Corticosteroids	34 (18.89)	18 (12.16)	16 (50.00)	**<0.001**[a]
Nutritional Supplements				
Zinc	129 (71.67)	107 (72.30)	22 (68.75)	0.686[b]
Vitamin D3	122 (67.78)	102 (68.92)	20 (62.50)	0.533[b]

[a] *Fisher's exact test*, [b] *Pearson's chi-squared test*, [c] *Mann-Whitney test*

Table 5. Association of Patient Characteristics and Need for ICU Admission

Clinico-demographic profile	Need for ICU admission			
	Total (n= 180)	Ward Only (n=144)	ICU Admission (n=36)	*p*-value
Demographic characteristics				
Age				
0-4	71 (39.44)	53 (36.81)	18 (50.00)	0.183[b]
5-9	30 (16.67)	24 (16.67)	6 (16.67)	
10-14	41 (22.78)	32 (22.22)	9 (25.00)	
15-18	38 (21.11)	35 (24.31)	3 (8.33)	
Sex				
Male	105 (58.33)	85 (59.03)	20 (55.56)	0.705[b]
Female	75 (41.67)	59 (40.97)	16 (44.44)	
Clinical characteristics				
COVID-19 Severity				
Asymptomatic	46 (25.56)	40 (27.78)	6 (16.67)	**<0.001[a]**
Mild	75 (41.67)	71 (49.31)	4 (11.11)	
Moderate	28 (15.56)	26 (18.06)	2 (5.56)	
Severe	17 (9.44)	6 (4.17)	11 (30.56)	
Critical	14 (7.78)	1 (0.69)	13 (36.11)	
Signs				
Fever	76 (42.22)	55 (38.19)	21 (58.33)	**0.029[b]**
Rales/Crackles/Rhonchi	37 (20.56)	18 (12.50)	19 (52.78)	**<0.001[b]**
Retractions	31 (17.22)	10 (6.94)	21 (58.33)	**<0.001[b]**
With signs of dehydration	21 (11.67)	11 (7.64)	10 (27.78)	**0.002[a]**
Alar flaring	18 (10.00)	5 (3.47)	13 (36.11)	**<0.001[a]**
Cyanosis	16 (8.89)	9 (6.25)	7 (19.44)	**0.021[a]**
Wheezing	7 (3.89)	3 (2.08)	4 (11.11)	**0.030[a]**
Symptoms				
Cough	49 (27.22)	30 (20.83)	19 (52.78)	**<0.001[b]**
Difficulty of breathing	42 (23.33)	18 (12.50)	24 (66.67)	**<0.001[b]**
Vomiting	35 (19.44)	32 (22.22)	3 (8.33)	0.060[b]
Poor suck / appetite	33 (18.33)	20 (13.89)	13 (36.11)	**0.002[b]**
Abdominal pain	29 (16.11)	28 (19.44)	1 (2.78)	**0.015[b]**
Colds	19 (10.56)	15 (10.42)	4 (11.11)	1.000[a]
Sore throat	2 (1.11)	1 (0.69)	1 (2.78)	0.361[a]
Watery stools	14 (7.78)	12 (8.33)	2 (5.56)	0.739[a]
Muscle pain	3 (1.67)	3 (2.08)	0 (0.00)	1.000[a]
Seizure	11 (6.11)	5 (3.47)	6 (16.67)	**0.009[a]**
Anosmia	1 (0.56)	1 (0.69)	0 (0.00)	1.000[a]
Ageusia	1 (0.56)	1 (0.69)	0 (0.00)	1.000[a]
Anthropometrics				
Height, cm	121 (82, 150)	131.5 (83, 152)	96.5 (78.25, 128.5)	**0.0430[c]**
Weight, kg	20.8 (9, 41.6)	25.5 (12, 44)	14 (8.5, 26)	**0.0098[c]**
Comorbidities				
Obese	4 (2.22)	3 (2.08)	1 (2.78)	1.000[a]
Asthma	2 (1.11)	1 (0.69)	1 (2.78)	0.361[a]
Tuberculosis	13 (7.22)	7 (4.86)	6 (16.67)	**0.025[a]**
Cardiac	21 (11.67)	14 (9.72)	7 (19.44)	0.143[a]
Hematologic / Oncologic	27 (15.00)	24 (16.67)	3 (8.33)	0.210[b]
Kidney	8 (4.44)	7 (4.86)	1 (2.78)	1.000[a]
Neurological	27 (15.00)	17 (11.81)	10 (27.78)	**0.016[b]**
Prematurity	2 (1.11)	2 (1.39)	0 (0.00)	1.000[a]
Gastrointestinal	27 (15.00)	25 (17.36)	2 (5.56)	0.076[b]
Genetic / Metabolic	3 (1.67)	1 (0.69)	2 (5.56)	0.102[a]
Endocrinologic	2 (1.11)	1 (0.69)	1 (2.78)	0.361[a]
Rheumatologic	3 (1.67)	3 (2.08)	0 (0.00)	1.000[a]
Immunologic	1 (0.56)	1 (0.69)	0 (0.00)	1.000[a]
Dengue Fever	2 (1.11)	2 (1.39)	0 (0.00)	1.000[a]
Healthcare-associated pneumonia	8 (4.44)	3 (2.08)	5 (13.89)	**0.009[a]**
Sepsis	7 (3.89)	5 (3.47)	2 (5.56)	0.628[a]

Table 5. Association of Patient Characteristics and Need for ICU Admission *(continued)*

Clinico-demographic profile	Need for ICU admission			
	Total (n= 180)	Ward Only (n=144)	ICU Admission (n=36)	*p*-value
Diagnostics				
CBC				
Hemoglobin	116 (39, 132)	116 (21, 134)	116 (96, 122)	0.9095[c]
Hematocrit	0.37 (0.33, 0.42)	0.37 (0.33, 0.43)	0.37 (0.32, 0.40)	0.3095[c]
White blood cells	11.5 (8, 15.8)	11.4 (7.8, 15.3)	13.3 (9.65, 17.62)	0.1569[c]
Neutrophils	0.67 (0.52, 0.81)	0.63 (0.49, 0.80)	0.78 (0.65, 0.83)	**0.0040[c]**
Lymphocytes	0.24 (0.11, 0.38)	0.26 (0.12, 0.40)	0.17 (0.10, 0.32)	**0.0457[c]**
Platelets	328 (231, 417)	328 (242, 413)	333 (221, 446)	0.8225[c]
ABG				
pH	7.41 (7.32, 7.45)	7.41 (7.36, 7.43)	7.42 (7.30, 7.47)	0.8536[c]
$PaCO_2$	30 (24, 39)	31 (28, 40)	28 (20, 38)	0.1353[c]
HCO_3	20.3 (14, 23.5)	20.6 (19.3, 25.3)	19.05 (13.1, 22.8)	0.2036[c]
PaO_2	110 (73, 167)	83 (43, 112)	126.5 (95, 176)	0.0654[c]
Other tests				
D-dimer	2.83 (1.01, 4.23)	1.80 (0.68, 3.17)	3.32 (1.32, 5.26)	**0.0444[c]**
Ferritin	226.5 (82.6, 686)	172.5 (82.6, 339)	404.5 (81.4, 1066.5)	0.3198[c]
CRP	22.63 (6, 96)	22.63 (6, 96)	18 (7, 169)	0.1904[c]
ESR	52 (11, 76)	48 (4.33, 65)	73.5 (41.5, 96.5)	0.1649[c]
Procalcitonin	0.28 (0.09, 2.93)	0.18 (0.09, 2.62)	0.72 (0.20, 4.35)	**0.0359[c]**
AST	64 (38, 117)	45 (34, 75)	94.5 (46.5, 177)	**0.0302[c]**
ALT	35 (20, 93)	23 (17, 57)	44 (24.5, 96.5)	0.0617[c]
LDH	451.5 (329, 897)	427 (334, 679)	565 (308, 990)	0.5475[c]
Creatine Kinase	94 (44, 653)	82 (29.5, 430)	150.5 (54.5, 976)	0.4592[c]
IL-6	94.5 (26.5, 389)	97.5 (17.5, 382.5)	94.5 (39, 646)	0.5881[c]
PT	14.8 (13.2, 22.3)	13.65 (12.7, 14.8)	16.7 (13.2, 24.0)	0.0811[c]
INR	1.20 (1.05, 1.43)	1.10 (1.01, 1.20)	1.3 (1.06, 1.50)	0.1482[c]
aPTT	30.9 (26.8, 35.7)	28.5 (25.6, 31.6)	32.6 (27.4, 38.8)	0.0667[c]
Imaging				
Chest x-ray, abnormal	92 (57.86)	62 (50.41)	30 (83.33)	**<0.001[b]**
Chest CT scan, abnormal	28 (100.00)	16 (100.00)	12 (100.00)	-
Therapeutics				
Investigational Drugs				
Oseltamivir	180 (100.00)	144 (100.00)	36 (100.00)	-
Remdesivir	8 (4.44)	1 (0.69)	7 (19.44)	0.001[a]
Tocilizumab	2 (1.11)	1 (0.69)	1 (2.78)	0.361[a]
Enoxaparin	1 (0.56)	0 (0.00)	1 (2.78)	0.200[a]
Antimicrobials				
Azithromycin	19 (10.56)	11 (7.64)	8 (22.22)	**0.028[a]**
Other antimicrobials	110 (61.11)	80 (55.56)	30 (83.33)	**0.002[b]**
IVIG	10 (5.56)	4 (2.78)	6 (16.67)	**0.005[a]**
Corticosteroids	34 (18.89)	11 (7.64)	23 (63.89)	**<0.001[b]**
Nutritional Supplements				
Zinc	129 (71.67)	104 (72.22)	25 (69.44)	0.741[b]
Vitamin D3	122 (67.78)	99 (68.75)	23 (63.89)	0.577[b]

[a] *Fisher's exact test,* [b] *Pearson's chi-squared test,* [c] *Mann-Whitney test*

significantly different between the two groups. However, azithromycin (p = 0.002), IVIg (p <0.001), and corticosteroid (p <0.001) administration were significantly higher among mechanically ventilated patients. The proportion of patients who received other antimicrobials, vitamin D3, or zinc were not significantly different between the mechanically ventilated and non-mechanically ventilated patients.

Association of Patient Characteristics and Need for ICU Admission

Shown in Table 5 is the univariate analysis of association between the patients' clinico-demographic characteristics and need for ICU admission. Majority of the patients, 144 (80%), were admitted in the wards while only 36 (20%) were admitted in the ICU. Age and sex were not significantly associated with ICU admission, p-values 0.183 and 0.705, respectively. COVID-19 severity was significantly associated with ICU admission. Specifically, about 66% of the patients who were admitted in the ICU and five percent of patients who were admitted in the wards had severe to critical COVID-19. Among the signs, fever, rales/crackles/rhonchi, retractions, signs of dehydration, alar flaring, cyanosis, and wheezing were significantly associated with ICU admission. Similarly, the symptoms including cough, difficulty of breathing, poor suck/appetite, abdominal pain, and seizure were significantly associated with ICU admission. Vomiting, colds, sore throat, watery stools, muscle pain, anosmia, and ageusia were not significantly associated with ICU admission. There was a statistically significant difference in the median height and weight of patients who were admitted in the wards and ICU. Specifically, patients who were admitted in the latter were shorter (96.5 kg versus 131.5 kg) and lighter (14 kg versus 25.5 kg), p = 0.0430 and 0.0098, respectively. Among the comorbidities, only tuberculosis and healthcare-associated pneumonia were significantly associated with ICU admission, p = 0.025 and 0.009, respectively. Furthermore, patients with COVID-19 who were admitted in the ICU had significantly higher neutrophil count, lower lymphocyte count, higher d-dimer levels, higher procalcitonin, and higher AST. The results of other laboratory tests were not significantly different between ward and ICU-admitted patients. The proportion of patients with abnormal chest x-ray findings was significantly higher among ICU-admitted patients, 83.33% versus 50.41%, p <0.001. There was no statistically significant difference in the proportion of patients with abnormal chest CT scan findings between the ward-admitted and ICU-admitted patients. Among the investigational drugs, the proportion of patients who received oseltamivir, tocilizumab, or enoxaparin were not significantly different between ward-admitted and ICU-admitted patients. However, the proportion of patients who received remdesivir was significantly higher among ICU-admitted patients, 19.44% versus 0.69%, p = 0.001. Similarly, the proportion of patients who received azithromycin (p = 0.028), other antimicrobials (p = 0.002), IVIG (p = 0.005), and corticosteroids (p <0.001) were significantly higher among ICU-admitted patients. The proportion of patients who received vitamin D3 or zinc were not significantly different between ward-admitted and ICU-admitted patients.

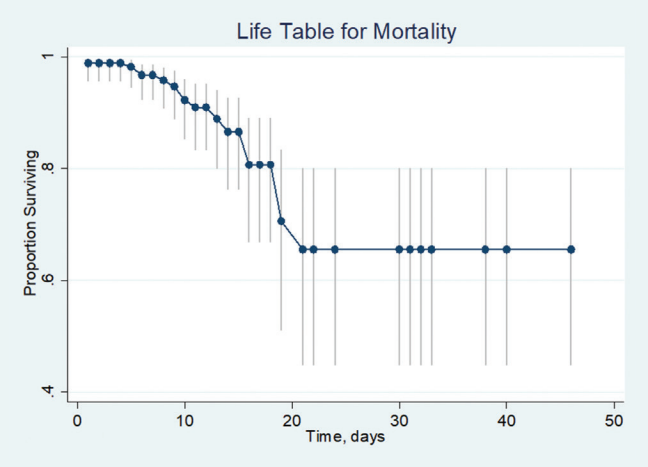

Figure 1. Life table for mortality, n=180.

Estimation of Survival Rates

A total of 176 unique observations were included in the estimation of survival. Four patients were excluded as they either died (2) or were discharged (2) on the same day of admission (i.e., observation time = 0). The median survival time was seven days (minimum of one day and maximum of 45 days). There were 15 mortalities and 1637 total analysis time at risk, which is equal to 9.2 mortality for every 1000 person-days contribution (95% CI: 5.5%, 15.2%). The life table for mortality is illustrated in Figure 1. This shows that from the first day to the fourth day of admission, 98.18% of patients were survivors. On the seventh day of admission, 95.56% of patients were survivors. On the 14th day of admission, only 85.91% of patients were alive. The survival flattens to 64.63% starting from the 20th day of admission up to the 45th day of admission.

Hazards of Mortality using Cox Proportional Hazards Regression

Crudely, age, sex, and comorbidity were not significantly predictive of mortality. However, patients with severe-critical COVID-19 severity had 11.51 times higher hazard of death as compared to patients who had lesser disease severity, p <0.001. Furthermore, patients who presented with retractions, alar flaring, cyanosis, difficulty of breathing, or poor suck/appetite during admission had a significantly higher hazard of death as compared to those who did not present with such signs and symptoms. Patients with seizure had 3.35 times probability of death but this was not statistically significant. Elevated levels of ferritin, IL-6, and aPTT were independently predictive of mortality. Specifically, for every unit increase in ferritin and IL-6, there was a 1% increased hazard of mortality whereas for every unit increase in aPTT,

there was a 5% increased hazard of mortality. Patients who received azithromycin had a 2.90 times increased hazard of mortality but this was not statistically significant. Patients who received IVIG or corticosteroids had four- and six-times increased hazard of mortality, p = 0.039 and 0.001, respectively. However, after controlling for the effects of age, sex, COVID-19 severity, comorbidity, signs and symptoms, and therapeutics, only retractions, alar flaring, seizure, and corticosteroids were significantly associated with mortality. Specifically, patients with retractions had almost 35 times increased hazard of mortality while those with seizure had almost 10 times increased hazard of mortality, p = 0.003 and 0.009, respectively. Interestingly, patients with alar flaring had 90% reduced hazard of mortality, p = 0.045, while patients who received corticosteroids had 8.21 times increased hazard of mortality, p = 0.039. The factors associated with mortality were summarized in Table 6 and the corresponding survival curves were shown in graphs (Appendix).

DISCUSSION

This study described the epidemiology and association of clinico-demographic profile with adverse outcomes of pediatric COVID-19 patients in a tertiary government COVID-19 referral hospital. Most of the patients were from the 0-4 age group, males, and had at least one comorbidity, and were classified as having mild COVID-19 disease. There was a small proportion of patients who died, underwent invasive mechanical ventilation, or got admitted in the ICU.

We found that chest retractions, alar flaring, cyanosis, difficulty of breathing, poor suck/appetite, seizure, IL-6, ferritin, aPTT, use of IVIg, and use of corticosteroids were independently predictive of mortality. However, upon controlling for the effects of other variables, only chest retractions, seizures, and use of corticosteroids were found to be significant hazards for mortality. To our knowledge, no similar study had utilized hazards for predicting the risk for mortality and other adverse outcomes for COVID-19 in children.

Findings of our study are consistent with global data that the most common reported signs and symptoms in children with COVID-19 are fever and respiratory symptoms.[7,12,17,23] This symptom pattern is similar with the adult population. Given this set of non-specific symptoms, COVID-19 is difficult to differentiate from other respiratory diseases, especially during the initial phase of the disease. No

Table 6. Hazards of Mortality using Cox Proportional Hazards Regression, n=180

Patient Characteristics	Hazard Ratio, crude (95% CI)	*p*-value	Hazard Ratio, adjusted (95% CI)	*p*-value
Age				
0-4, Ref				
5-9	0.88 (0.23, 3.31)	0.846	4.86 (0.67, 35.01)	0.117
10-14	0.60 (0.16, 2.30)	0.461	0.46 (0.10, 2.11)	0.318
15-18	0.34 (0.04, 2.72)	0.308	3.63 (0.23, 57.49)	0.361
Sex				
Male, Ref				
Female	1.62 (0.59, 4.48)	0.352	2.18 (0.56, 8.52)	0.261
COVID-19 Severity				
Asymptomatic, Mild, Moderate, Ref				
Severe-Critical	11.51 (3.23, 41.06)	**<0.001**	2.68 (0.28, 25.76)	0.393
With comorbidity	0.93 (0.30, 2.95)	0.912	0.58 (0.10, 3.21)	0.530
Signs and symptoms				
Retractions	10.30 (3.27, 32.47)	**<0.001**	34.96 (3.36, 363.79)	**0.003**
Alar flaring	4.39 (1.53, 12.58)	**0.006**	0.10 (0.01, 0.95)	**0.045**
Cyanosis	4.93 (1.72, 14.11)	**0.003**	4.59 (0.91, 23.18)	0.065
Difficulty of breathing	7.99 (2.25, 28.41)	**0.001**	0.35 (0.03, 3.88)	0.394
Poor suck / appetite	4.46 (1.59, 12.40)	**0.004**	2.87 (0.48, 16.96)	0.246
Seizure	3.35 (0.94, 11.88)	0.062	9.98 (1.76, 56.55)	**0.009**
Laboratory tests				
Ferritin (n=42)	1.01 (1.00, 1.01)	**0.004**	-	-
IL-6 (n=40)	1.01 (1.00, 1.01)	**0.023**	-	-
aPTT (n=26)	1.05 (1.01, 1.10)	**0.030**	-	-
Therapeutics				
Azithromycin	2.90 (0.99, 8.49)	0.053	3.94 (0.86, 18.00)	0.077
IVIG	4.00 (1.07, 14.92)	**0.039**	0.97 (0.12, 7.74)	0.979
Corticosteroids	6.01 (2.04, 17.67)	**0.001**	8.21 (1.12, 60.38)	**0.039**

Note: The full model for the adjusted Cox proportional hazards regression included the following covariates: age group, sex, COVID-19 severity dichotomized to severe-critical and asymptomatic-mild-moderate, comorbidity, retractions, alar flaring, cyanosis, difficulty of breathing, poor suck/appetite, seizure, azithromycin, IVIG, and corticosteroids. The laboratory tests including ferritin, IL-6 and aPTT, although eligible for inclusion in the adjusted Cox model, were excluded due to very few observations. The proportional hazards assumption global p-value was 0.6632 (i.e., the model is appropriate).

pathognomonic sign/symptom has been reported for SARS-CoV-2 infection to date. In other studies, the most common symptom presented by pediatric COVID-19 non-survivors was gastrointestinal particularly diarrhea[24] and this can also be the sole manifestation among them.[25] Moreover, one group reported that increased odds of in-hospital mortality was found in severe COVID-19 presenting with hypoxia on admission.[24] In our study, we highlight chest indrawing (retractions), alar flaring, and cyanosis as clinical signs most commonly presented by children who eventually died of COVID-19. Chest retractions and alar flaring were found to be statistically significant hazards predictive of mortality.

Most children in our study had mild disease (41.67%). This trend is similar to the results of several studies done in other countries. Globally, the number of children infected by SARS-CoV-2 is disproportionately lower compared with adults and the incidence of severe and critical COVID among children is low.[2,23] Chaiyakulsil et al. found that 2.3% of their pediatric COVID patients in Thailand were tagged as severe to critical, with the majority (53%) having mild disease.[21] Similarly, Wong et al. showed that across seven countries in Asia, only 10.2% of pediatric subjects were tagged as severe to critical, with infants being more likely to fall under this severity category.[23] This pattern is congruent with our findings where 64.29% of the critical COVID-19 patients were from the 0-4 years age group. To date, it is still unclear why children with COVID-19 have milder disease compared to adults. Theories about this disease pattern include immunosenescence or a decline in immune function with advanced age in contrast to the pediatric population, which is able to maintain normal white blood cell counts.[26]

The generally milder course of COVID-19 among children is typically correlated with a low mortality.[23,27] Children with COVID-19 have good prognosis and generally recover within 1-2 weeks after disease onset.[28] Majority of the mortalities in a study in India were among age 0-10 years (66.6%).[24] Another study in Mexico also reported that despite older children being more likely to have the disease, almost 50% of deaths occurred in children under 2 years.[27] These reports are consistent with the findings in our study where mortality occurred mostly in the 0-9 years age group (76.45%, n=17) compared to those in the 10-18 years age bracket. Interestingly, our results showed that age and COVID-19 severity together were not predictive of mortality. Independently, however, disease severity was found to be significantly associated with mortality.

One study found pulmonary or neurologic comorbidities plus renal or hepatic dysfunctions to be associated with mortality[17] while increased odds of in-hospital mortality was found in severe COVID-19 who had three or more affected organ systems, acute kidney injury, thrombocytopenia, and elevated CRP[24]. In one multivariate analysis, concurrent pneumonia, seizures, and hepatic injury were associated with higher mortality[17]— which contrast with our results. Furthermore, in that study, dexamethasone had no significant association with mortality while mucocutaneous symptoms, use of methylprednisolone and/or IVIg or anticoagulation, and having MIS-C were associated with lower mortality.[17]

Common comorbid conditions among children with COVID-19 reported were chronic kidney disease (CKD)[29], hematologic and immune disorders, respiratory disorders, and cardiovascular diseases[30]. Among adolescents, the most common comorbid conditions were obesity, neurologic diseases, and pulmonary diseases (excluding mild asthma).[31] A systematic review and meta-analysis of 42 studies reported that childhood obesity was likely associated with worse COVID-19 outcomes due to the potential of high visceral adiposity to induce systemic inflammatory cytokines.[32,33] In contrast to the previous studies, our results showed that hematologic-oncologic disorders, particularly Acute Lymphoblastic Leukemia, are the most common comorbidities of pediatric COVID-19 patients. Patients with cancer are thought to be susceptible to contracting COVID-19 and those with hematologic malignancies have poorer prognoses than those with solid tumors.[34]

Children with COVID-19 who presented with seizures were found in this study to have almost 10 times increased risk of mortality compared to those who did not present with seizures. Data suggest that the central nervous system (CNS) has some immunomodulatory function through the cholinergic anti-inflammatory pathway. Consequently, CNS dysfunctions including ictal and interictal autonomic dysfunctions in epilepsy have effects on immune response.[35]

The utilization of corticosteroids has been studied in 2020 among critically-ill adult COVID-19 patients and it was found to be associated with a lower 28-day all-cause mortality.[36,37] A separate meta-analysis in 2021, however, revealed delayed viral clearance with the use of corticosteroids. Moreover, they found that there was no significant difference between the survivors and non-survivors in terms of corticosteroid use.[38] Consistent with the latter study, our results showed that the use of corticosteroids among COVID-19 pediatric patients is associated with an 8-fold increase in the risk of mortality from baseline. After controlling for other variables such as COVID-19 severity, presence of comorbidities, and laboratory parameters, we found corticosteroids to be a significant hazard for mortality. There is a scarcity of clinical studies on the use of corticosteroids among pediatric COVID-19 patients, and its benefits and risks are uncertain. The World Health Organization recommends systemic glucocorticoids for adult patients with severe or critical COVID-19. However, the applicability for children is uncertain because of lack of evidence. The United States National Institutes of Health (US NIH) recommends dexamethasone for pediatric COVID-19 patients who are only high-flow oxygen-requiring, mechanically ventilated, on extracorporeal membrane oxygenation (ECMO), or on non-invasive ventilation.[39]

A study done on non-ICU SARS-CoV cases showed that early initiation of steroids resulted in significantly higher

plasma SARS-CoV RNA levels.[40] COVID-19-associated respiratory distress presents as diffuse alveolar damage hence steroids are thought to decrease the lung inflammation. However, we associate the harm observed in children with COVID-19 who were given corticosteroids with the drug's capability to inhibit immune response and subsequent clearance of the SARS-CoV-2.

CONCLUSIONS

Majority of hospitalized pediatric COVID-19 patients were very young, males, had mild disease, and had at least one comorbidity. Mortality, invasive mechanical ventilation, and ICU admission were relatively low. Except for alar flaring which appeared to be protective, retractions, seizure, and use of corticosteroids were associated with adverse outcomes.

Limitations and Biases

Due to the retrospective nature of the study, the data gathered were limited to the retrievable registry of COVID-19 patients of the Philippine General Hospital provided by the Pediatric Infectious Disease Society of the Philippines, Inc. Moreover, the outcomes of the variables studied were dependent on the accuracy of reporting and documentation in the said registry. Although an increasing value of ferritin, IL-6, and aPTT were significantly associated with mortality in the crude analysis, these, as well as pH were not included in the adjusted Cox regression analysis because of limited number of subjects, ranging from 26-42. These tests were not routinely ordered in the said hospital unless the patients had severe disease presentation on admission.

Data Access

Data was collected from the Pediatric Infectious Disease Society of the Philippines, Inc. registry. The registry is maintained by PIDSP Inc. and can be accessed online at: https://salvacion.pidsphil.org/. The registry contains anonymized data.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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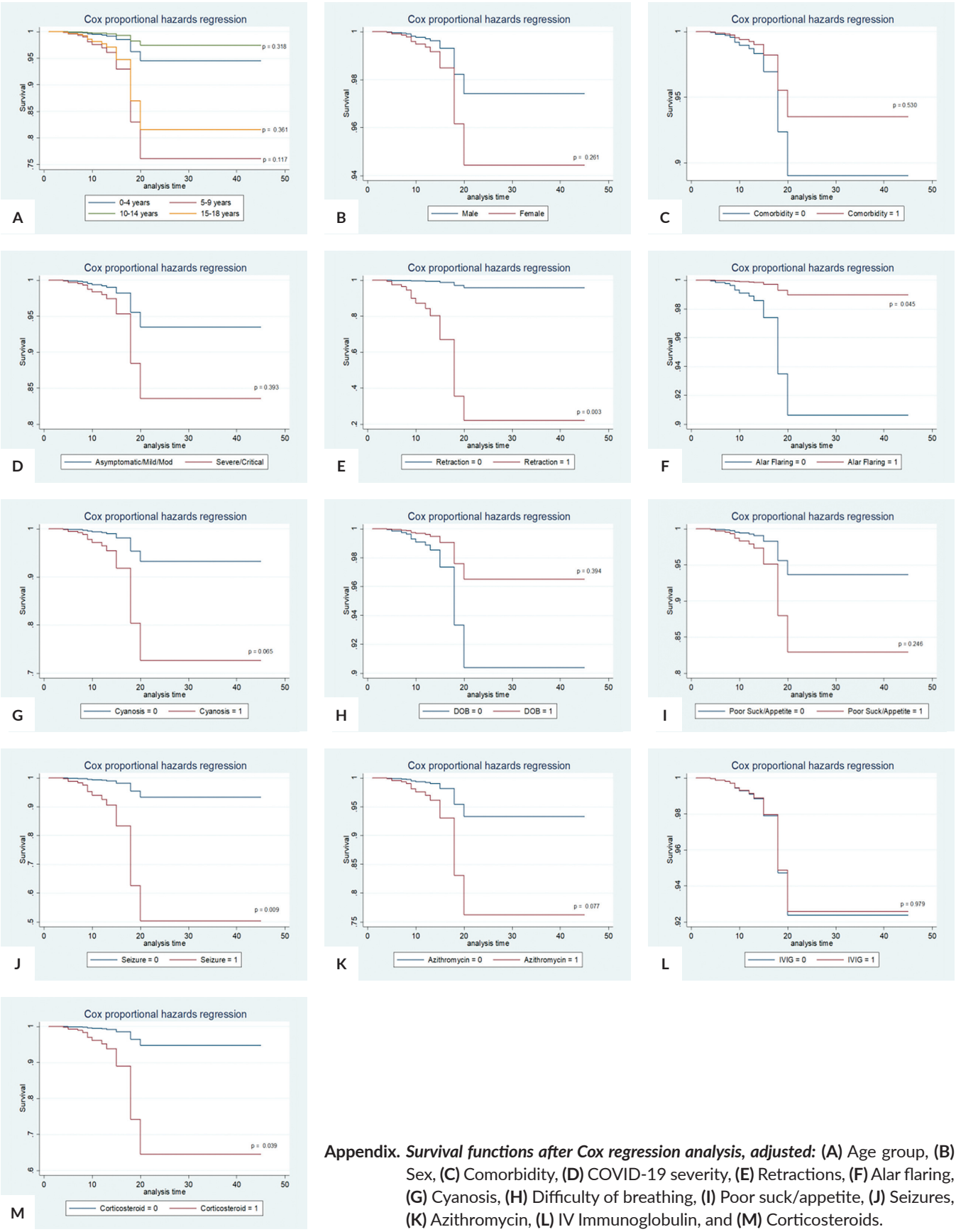
APPENDIX



Appendix. ***Survival functions after Cox regression analysis, adjusted:*** **(A)** Age group, **(B)** Sex, **(C)** Comorbidity, **(D)** COVID-19 severity, **(E)** Retractions, **(F)** Alar flaring, **(G)** Cyanosis, **(H)** Difficulty of breathing, **(I)** Poor suck/appetite, **(J)** Seizures, **(K)** Azithromycin, **(L)** IV Immunoglobulin, and **(M)** Corticosteroids.