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Original Article

Risk factors for disease severity and mortality of children with Covid-19: A study at a Vietnamese Children's hospital

Phung Nguyen The Nguyen [a,b,*], Tran Thanh Thuc [a,b], Nguyen Thanh Hung [b], Le Quoc Thinh [b], Ngo Ngoc Quang Minh [b], Dang Quoc Duy [b], Tran Minh Nhut [a], Nguyen Bich Y Linh [a], Tran Minh Tuan [a], Ngo Hoang Lam Giang [a], Vo Thi Minh Tuyen [a]

[a] University of Medicine and Pharmacy at Ho Chi Minh City, Viet Nam
[b] Children's Hospital 1, Ho Chi Minh City, Viet Nam

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ABSTRACT

Introduction: To find out risk factors for disease severity and mortality of pediatric COVID-19 in the fourth wave of COVID-19 in Vietnam.

Methods: This retrospective cohort study was performed at Children's Hospital 1 from July to December 2021. All children with COVID-19 confirmed by a positive Realtime RT-PCR SARS-CoV-2 result and treated at COVID-19 department for at least 72 h were included.

Results: Of the 850 cases admitting to COVID-19 department, 555 children with COVID-19 confirmed by positive RT-PCR and treated at our center for more than 72 h. Median age of confirmed cases was 22.3 (IQR: 3.2–88.6) months, 55.1% were male, and 84.5% had a history of close contact with confirmed COVID-19 patients. The rate of mild, moderate and severe/critical cases was 73,7%, 9.0% and 17.3%, respectively. One hundred ninety-two children (34.6%) had underlying diseases, in which, neurologic disease was the most common underlying disease (7.9%). Underlying disease, dyspnea, elevated CRP >20 mg/L and elevated ferritin were independent factors related to severe illness. Twenty-point two percent of patients in our study needed respiratory support, including 22 invasive mechanical ventilation cases. Eighteen cases (3.2%) died because of severe comorbidities, poor response to treatment.

Conclusions: In our study, the severe/critical and mortality rates in pediatric COVID-19 cases were relatively high. All fatal cases had severe comorbidities. Underlying disease, dyspnea, and elevated inflammatory markers were independent factors related to severity in pediatric COVID-19 cases.

1. Introduction

Since it was first identified in late December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes the coronavirus disease 2019 (COVID-19), has spread around the world and become a serious health problem in various countries, including Vietnam [1,2]. Vietnam has experienced different waves of COVID-19 epidemic, of which the 4th one that started in May until the end of 2021 has been the most serious, both in terms of the number of infections and the number of severe, fatal cases. As of December 31, 2021, Vietnam has recorded 1,731,257 infections and 32,394 deaths from COVID-19 [3]. Children are also subjects to infection with SARS-CoV-2. Our hospital is one of the tertiary care centers, receiving and treating children with mild to critical COVID-19.

COVID-19 symptoms in children are similar to those in adults, but their frequency is different [4–6]. Besides, the signs and symptoms of COVID-19 in children are similar to those of other infectious or non-infectious diseases [7]. The lack of specificity of signs and symptoms and the significant proportion of asymptomatic infections make symptom-based screening for SARS-CoV-2 infection in children particularly difficult [7,8]. Although most children with COVID-19 have mild symptoms or no symptoms at all, some of them, especially children with underlying medical conditions, become severely ill needing hospitalization, intensive care, or ventilatory support [9,10]. Several factors related to severe disease progression in children with COVID-19 have been identified, such as comorbidities (e.g. congenital heart diseases,

* Corresponding author. Chair of Department of Pediatrics, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam, 217 Hong Bang Street, District 5, Ho Chi Minh City, Viet Nam.
E-mail address: nguyenphung@ump.edu.vn (P.N.T. Nguyen).

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immunodeficiency), co-infection, hypoxemia, highly elevated CRP [11–13]. Up to now, the medical literature has not provided sufficient data on treatments for COVID-19 in children [5,14]; most of which are still based on the results of studies in adult, so the quality of evidence is low. Moreover, the change in national epidemic strategy and treatment guidelines and the availability of therapeutic drugs also affect the treatment of COVID-19 in children in different countries. Mortality rates for COVID-19 in children also varied across studies, although most of them were lower than in adults [11,15]. Therefore, we believe that the data on characterization of severe COVID-19 in Vietnamese children and identifying risk factors for pediatric severe COVID-19 are helpful for the management of COVID-19 in children.

2. Patients and methods

We performed a retrospective cohort study at Children's Hospital 1 (CH1) from July 25 to December 31, 2021. All children with indications for hospitalization for COVID-19 or other causes, are screened by antigen testing, if the child or caregiver is positive for COVID-19, the child is admitted to the COVID-19 ward. The antigen rapid test used at our hospital is the Panbio™ COVID-19 Ag Rapid Test Device from Abbott. After then, SARS-CoV-2 infection condition would be confirmed by Realtime Reverse Transcription - Polymerase Chain Reaction (RT-PCR) test within 24 h after admission. Patients hospitalized for suspected COVID-19 but had negative RT-PCR results were excluded. All the children with COVID-19 confirmed by a positive RT-PCR SARS-CoV-2 result and treated at our center for at least 72 h were included. We included children treated for 3 days or more because in these children, we have detailed clinical, laboratory data and results of treatment. We excluded children transferred to other hospitals within 3 days due to overcrowding.

The nasopharyngeal specimen was repeated after 7 days of admission to consider whether the patient is eligible for discharge according to the guideline of the Ministry of Health of Vietnam (Cycle threshold value $>$ 30). Nasopharyngeal specimens were collected using Xpert FLOQSwabs® kit (COPAN Italia). The nasopharyngeal specimens were then fixed in the solution of Liofilchem s.r.l.. Nucleic acid extraction and RT-PCR were performed on CFX96 Touch Real-Time PCR Detection System (BIO-RAD) and Realtime PCR Rotor-Gene Q MDx (QIAGEN). The target genetic region for RT-PCR SARS-CoV-2 test in our hospital was E gene. RT-PCR was performed according to the procedures of the Microbiology department, CH 1 (validated and licensed by the Vietnam Ministry of Health).

Patient charts were reviewed to collect data on patient demographics, clinical history, significant underlying chronic comorbidities, clinical manifestations, laboratory investigations, and medical management. Daily symptoms as reported in the admission and progress notes were recorded.

Disease severity categorization was based on pediatric COVID-19 guidelines of the Ministry of Health of Vietnam (Appendix A). We classified patients into 3 areas according to degree of severity. Severe/critical patients were treated in the intensive care rooms. Patients who either were moderate or had underlying disease requiring monitoring were treated in the emergency rooms. Finally, mild children accompanied by their parents were treated in the regular rooms. We perform examination and follow-up depending on the severity of the disease, at least twice a day. Results of laboratory investigations and chest radiography done at admission were collected. All patients were routinely tested including complete blood count, C-reactive protein, ferritin at the time of admission. Chest X-ray was taken when pneumonia was suspected. Moderate and severe cases would be further tested for liver function, kidney function and complete coagulation status.

Biochemical tests were performed by BECKMAN COULTER AU-680 machine at the Department of Biochemistry, CH 1. The total blood count and coagulation test were peformed by the Sysmex XN-2000 and STA R-Max machine, respectively, at the Department of Hematology Laboratory, CH 1. The coagulation test was performed within 30 min after taking the sample for the most reliable result. Chest X-ray results were evaluated by radiologist of CH 1.

Differences between the mild-moderate and severe/critical groups were analyzed using Fisher's exact test/Chi-square test for categorical variables and Student's t-test/Wilcoxon Rank Sum test for continuous variables. Multivariable logistic regression analysis was used to find out factors associated with disease severity and mortality. Statistical analysis was conducted through STATA 14, and a two-tailed $p < 0.05$ was considered statistically significant.

Ethics: This study was approved by the ethics committee of the Children's Hospital 1 with research code is CS/N1/21/65.

3. Results

From July 2020 to the end of December 2021, we received and treated 850 children suspected or confirmed SARS-CoV-2 infection. Among them, 555 children with COVID-19 confirmed by positive RT-PCR and treated at our center for more than 72 h. We did not sequence the genes to identify the SARS-CoV-2 virus variant, however the predominant strain circulating in Vietnam during this period was the Delta variant. The study flow chart was shown in Fig. 1.

The median age in our study group was 22.3 months, of whom the youngest was 2 days old and the oldest was 16 years old. The male/female ratio is 1.23. The number of boys and girls has no statistically significant difference. Eighty-four-point five percent of the study group had a history of close contact with confirmed COVID-19 patients or those were from a family-cluster.

In our study, the proportions of mild, moderate and severe/critical cases were 73.7%, 9.0% and 17.3%, respectively. The rate of moderate and severe/critical clinical presentation was highest among the children older than 11 years. Clinical severity, according to age, was shown in Fig. 2. There were 15 cases in the severe group aged 12–16 years old. From the late November 2021, Vietnam started a program of vaccination against COVID-19 for children over 12 years old. The COVID-19 vaccines used for children over 12 years old in Vietnam was Pfizer-BioNTech.

Clinical symptoms of the study group were described in Table 1. Fever was the most prominent symptom with an average temperature of 38.5 ± 0.34 (^{o}C). Besides, we recorded that 26.2% of the children older than 6 years old had loss of smell/taste symptom. Comorbidities were identified in 192 children (34.6%). Neurologic disease was the most common comorbidities, in 7.9% of cases, followed by obesity (6.1%), kidney diseases (4.3%), hematologic disease (4.0%), gastrointestinal - hepatic diseases (3.4%), congenital heart diseases (3.2), respiratory diseases (2.3%). Other underlying medical conditions include: prematurity, congenital metabolic disorders, congenital immunodeficiency, severe malnutrition.

Leukocytosis was present in 35 patients (6.3%), lymphopenia and thrombocytopenia were very rare in study group. Increased levels of C-reactive protein (CRP) and ferritin were identified in 18% and 72.1% patients, respectively as shown in Table 2. The highest AST and ALT levels recorded were 3011 and 726, respectively. Both values were recorded in the one patient and this patient was diagnosed with septic shock - multiple organ failure - critical COVID-19. Five patients had high creatinine levels, all of them had been diagnosed as suffering chronic kidney disease. D-dimer parameter were performed in 146 patients and 27 (18.5%) patients had high D-dimer levels more than 5 times of normal. We used multivariable logistic regression analysis to find the related factors between the mild - moderate group and severe/critical group. Underlying disease and dyspnea were two clinical factors independently related to severe illness, with OR of 3.1 (95%CI: 1.37–6.99, $p = 0.006$) and 57.1 (95%CI: 20.6–157.7, $p < 0.001$). From a subclinical perspective, elevated ferritin and CRP >20 mg/L were two independent factors related to severity with OR 3.4 (95%CI: 1.18–9.73, $p = 0.02$) and 3.92 (95%CI: 1.46–10.6, $p = 0.007$) (Table 3). The patients from

RISK FACTORS FOR DISEASE SEVERITY AND MORTALITY OF CHILDREN WITH COVID-19: A STUDY AT A VIETNAMESE CHILDREN'S HOSPITAL

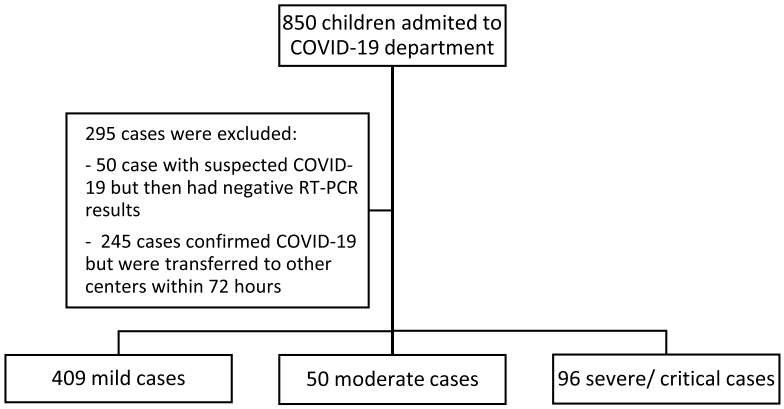

Fig. 1. Study flow chart.

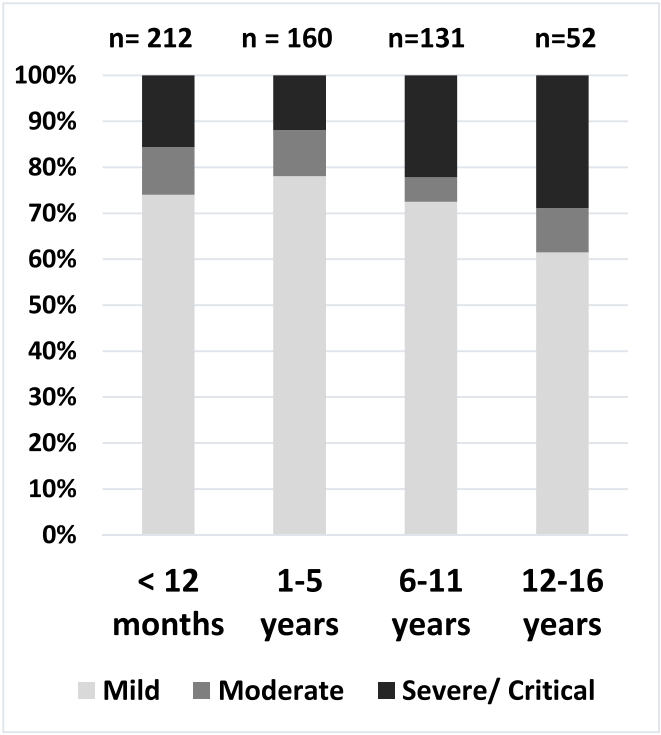

Fig. 2. Clinical severity, according to age in the study group.

moderate to severe group in our study had chest X-rays and recorded lesions on chest X-rays. The predominant lesion on chest X-rays was interstitial lesion (78.1%). There were 60 patients with pulmonary parenchymal consolidation, of which 48 were in the severe group. Pleural effusion and pneumothorax were encountered in 7 and 4 cases, respectively.

Respiratory support was required in 112 patients. In which, the most was cannula oxygen (67 patients), followed by mechanical ventilation, high flow nasal cannula (HFNC)/nasal continuous positive airway pressure (NCPAP) and non-invasive ventilation in 27, 17 and 7 patients, respectively. Four case needed cannula oxygen in the mild group, of which three were hospitalized for severe laryngotracheobronchitis (croup) and one for dengue shock. Dengue fever is one of the most common diseases in Vietnam. However, in our study population, only 8 cases of dengue fever and COVID-19 co-infection were recorded. Of those, seven cases are mild dengue fever, and only one case is shock. This case required oxygen as described, and oxygen was given in this case as

Table 1
Clinical characteristics of the study groups.

Characteristics	Total (n = 555)	Mild - moderate (n = 459)	Severe/ critical (n = 96)	*p*-value
Age, months (median, IQR)	22.3 (3.2–88.6)	21.0 (2.9–80.7)	38.7 (5.9–113.9)	**0.03**
Male (n, %)	306 (55.1)	248 (54.0)	58 (60.4)	0.25
Female (n, %)	249 (44.9)	211 (46.0)	38 (39.6)	
Family history/close contact (n, %)	469 (84.5)	392 (85.4)	77 (80.2)	0.20
Underlying disease (n, %)	192 (34.6)	134 (29.2)	58 (60.4)	**<0.001**
None	363 (65.4)	325 (70.8)	38 (39.6)	
Neurologic disease	44 (7.9)	29 (6.3)	15 (15.6)	**0.002**
Congenital heart disease	18 (3.2)	11 (2.4)	7 (7.3)	**0.014**
Respiratory disease	13 (2.3)	9 (2.0)	4 (4.2)	0.25
Gastrointestinal - hepatic disease	19 (3.4)	11 (2.4)	8 (8.3)	**0.004**
Kidney disease	24 (4.3)	20 (4.4)	4 (4.2)	0.93
Hematologic disease	22 (4.0)	20 (4.4)	2 (2.1)	0.40
Obesity[a]	34 (6.1)	14 (3.1)	20 (20.8)	**<0.001**
Others	27 (4.9)	20 (4.4)	7 (7.3)	–
Clinical symptoms (n, %)				
Fever[b]	430 (77.5)	344 (74.9)	86 (89.6)	**0.002**
Cough	283 (51)	201 (43.8)	82 (85.4)	**<0.001**
Dyspnea/ Tachypnea	129 (23.2)	44 (9.6)	85 (88.5)	**<0.001**
Runny nose	100 (18.0)	77 (16.8)	23 (24)	0.09
Sore throat	37 (6.7)	21 (4.6)	16 (16.7)	**<0.001**
Vomiting	107 (19.3)	89 (19.4)	18 (18.8)	0.89
Diarrhea	101 (18.2)	74 (16.1)	27 (28.1)	**0.006**
Stomachache	56 (10.1)	46 (10.0)	10 (10.4)	0.91
Convulsion	60 (10.8)	48 (10.5)	12 (12.5)	0.56

[a] Obesity: weight for height >+3SD in children under 5 years old or BMI for age >+2SD in children over 5 years old.
[b] Fever is defined as axillary temperature higher than 38 °C.

Table 2
Laboratory characteristics of the study groups.

Parameters	Normal range (units)	Total (n = 555)	Mild - moderate (n = 459)	Severe/critical (n = 96)	*p*-value
WBC count (median, IQR)	4.0–12.0 (x10^3/μL)	8.2 (6.1–11.1)	8.1 (6.2–10.9)	8.8 (5.8–11.8)	0.67
Neutrophil count	3.0–5.8 (x10^3/μL)	3.2 (1.8–5.4)	3.0 (1.8–5.0)	3.9 (2.1–7.4)	**0.004**
Lymphocyte count	1.5–3.0 (x10^3/μL)	3.3 (2.0–4.8)	3.4 (2,1–4.8)	2.8 (1.8–4.6)	0.05
Platelet count (median, IQR)	150–400 (x10^3/μL)	280 (215–353)	287 (220–355)	248 (193–332)	0.05
CRP (median, IQR)	<5 (mg/L)	3.3 (0.7–14.2)	2.6 (0.7–10.6)	8.6 (1–56.8)	**<0.001**
CRP > 20 mg/L (n, %)		100 (18.0)	61 (13.3)	39 (40.6)	**< 0.001**
Ferritin (median, IQR)	6–60 (μg/L)	251.7 (84.3–542)	166.8 (67.6–443)	488.6 (271.5–783.4)	**<0.001**
Elevated ferritin (n, %)		400 (72.1)	311 (67.8)	89 (92.7)	**< 0.001**
E gene Ct value (mean ± variance)		22.6 ± 7.1	22.2 ± 7.1	24.5 ± 6.9	**0.01**
		Total (n = 146)	**Moderate (n = 50)**	**Severe/critical (n = 96)**	
AST (median, IQR)	**15–60 (U/L)**	**55.5 (43.5–89.7)**	**45.7 (38–60.3)**	**60.5 (48–103.7)**	0.001
ALT (median, IQR)	13–45 (U/L)	31.7 (22.4–51.4)	28.3 (21–38.1)	37 (22.7–69.8)	**0.02**
Creatinine (median, IQR)	35.0–62.0 (μmol/L)	42.7 (35.1–51.9)	36.6 (32–42.2)	46.0 (38.6–53.8)	**<0.001**
PT (median, IQR)	13.1–16.3 (s)	13.6 (12.4–15.2)	13.2 (12.3–14.4)	13.8 (12.6–15.6)	0.07
PT > 18s (n, %)		17 (11.6)	4 (8)	13 (13.5)	0.42
aPTT (median, IQR)	28.6–35.8 (s)	34.1 (30.7–39.4)	35.5 (31.3–39.5)	33.2 (30.5–38.7)	0.58
aPTT > 44s (n, %)		17 (11.6)	5 (10)	12 (12.5)	0.66
Fibrinogen (median, IQR)	2.03–3.77 (g/L)	3.1 (2.4–4.3)	3.7 (2.9–4.5)	2.9 (2.3–4.0)	**0.009**
D-dimer (median, IQR)	0.09–0.53 (μg/mL)	0.9 (0.63–1.78)	0.72 (0.56–1.12)	1.14 (0.67–2.17)	**0.02**
D-dimer > 5ULN (n, %)		27 (18.5)	6 (12)	21 (21.9)	0.15

WBC: white blood cell, CRP: C-reactive protein, Ct: Cycle threshold.
AST: aspartate aminotransferase; ALT: alanine aminotransferase; PT: prothrombin time; aPTT: activated partial thromboplastin time.

Table 3
Multivariable logistic regression analysis to find the independent factors related to severity.

Characteristics	Odd ratio	p-value	95% Confident Interval	
Age	1.002	0.61	0.995	1.009
Underlying disease	**3.10**	**0.006**	**1.37**	**6.99**
Fever	0.92	0.89	0.28	3.04
Cough	1.23	0.7	0.43	3.52
Dyspnea	**57.1**	**<0.001**	**20.6**	**157.7**
Neutrophil count	0.99	0.88	0.91	1.08
CRP > 20 mg/L	**3.92**	**0.007**	**1.46**	**10.6**
Elevated ferritin	**3.4**	**0.02**	**1.18**	**9.73**
E gene Ct value	1.04	0.12	0.99	1.10

an adjunctive therapy in the management of shock and not because of lung injury from COVID-19. There was one infant in the mild group hospitalized with severe congenital heart disease (tricuspid valve atrophy - right ventricular hypoplasia) and the child needed mechanical ventilation for cardiovascular intervention. After 7 days of admission, the child was detected to be positive for SARS-CoV-2. Fortunately, at that time, the child was weaned off from the mechanical ventilation and no lung damage was seen on the chest X-ray. The median duration of respiratory support in the study was 6 (IQR: 4–9) days. Corticosteroids was used in 138 cases (24.9%) with the mean duration of treatment was 8.5 days. There were 20 patients in the mild group treated with corticosteroids. However, the use of corticosteroids in these children was not for the purpose of treating COVID-19, but for treating croup. Anticoagulation was used in 83 severe and 20 moderate cases. Thirteen cases in the severe group were not given anticoagulation because of contraindications such as severe coagulopathy, thrombocytopenia, and so on. The median duration of anticoagulation was 9 (IQR: 7–11) days. Fifty-eight-point seven percent of the cases in the study were given antibiotics because of severe disease or the bacterial co-infection could not be ruled out. Antibiotic groups were used including oral amoxicillin - clavulanic acid, third generation cephalosporin, carbapenem, vancomycin and quinolone. Also, there were 5 cases coinfection confirmed as bacterial infection by blood culture, including 2 with *Staphylococcus aureus*, 2 with *E. coli* and 1 with *Stenotrophomonas maltophilia*. Of the 5 bacteremia infections in our study, only 1 case of community-acquired *Staphylococcus aureus* infection, blood culture was obtained at the time of admission. The remaining 4 cases were all healthcare-associated infections. These cases were cases of prolonged hospitalization due to comorbidities (cirrhosis, cerebral palsy, congenital heart disease) and blood cultures were obtained after 48 h of hospital stay. The antiviral drug used in our study, as well as in Vietnam, was remdesivir. There were 46 cases of receiving remdesivir, 42 cases in the severe group and 4 cases in the moderate group.

The mortality rate in the study was 3.2%. Table 4 describes the differential characteristics between the death and survival patients in the severe group. All fatal cases had severe comorbidities, these children were hospitalized because of SARS-CoV2 infection with a pre-existing medical condition such as nephrotic syndrome, severe congenital heart disease, neurologic disease, immunodeficiency, and so on. All these cases were treated promptly as severe COVID-19 with anti-inflammatory, anticoagulant and antiviral when indicated and not contraindicated. However, these cases still progressed gradually, poorly responding to specific treatment. The direct cause of death in most of these children was due to severe comorbidities. Characteristics of each case in the death group were described in the Appendix B. In the severe

Table 4
Differential features between the death and survival in the severe group.

	Death (n = 18)	Survival (n = 78)	*p* - value
Age (median, IQR)	15.4 (3–98)	49.7 (6–120)	0.21
Male (n, %)	8 (44.4)	50 (64.1)	0.124
Underlying disease (n, %)	18 (100)	45 (57.7)	**<0.001**
Fever (n, %)	15 (83.3)	71 (91.0)	0.39
Dyspnea/Tachypnea (n, %)	14 (77.8)	71 (91.0)	0.21
WBC > 12 k/mm^3 (n, %)	11 (61.1)	12 (15.4)	**<0.001**
NEU[a] > 10 k/mm^3 (n, %)	6 (33.3)	4 (5.1)	**0.003**
CRP (median, IQR)	53.6 (6.6–172.2)	5.6 (0.7–41.6)	**0.02**
CRP > 20 mg/L (n, %)	10 (55.6)	29 (37.2)	0.152
Ferritin (median, IQR)	543.3 (287.5–837.2)	474.2 (249.6–780.5)	0.63
Elevated ferritin (n, %)	15 (83.3)	74 (94.9)	0.12
D-dimer (median, IQR)	1.7 (0.8–2.8)	1.1 (0.6–1.8)	**0.04**
D-dimer > 5 ULN[b] (n, %)	10 (55.6)	23 (29.5)	**0.04**
Respiratory support (n, %)	18 (100)	75 (96.2)	0.53
Anticoagulant (n, %)	10 (55.6)	73 (93.6)	**<0.001**
Corticosteroids (n, %)	12 (66.7)	78 (100)	**<0.001**
Remdesivir (n, %)	3 (16.7)	39 (50.0)	**0.02**
Antibiotics (n, %)	18 (100)	77 (98.7)	0.81

[a] NEU: Neutrophil.
[b] ULN: Upper Limit of Normal.

group, the patients without medical underlying disease had no deaths.

4. Discussion

This is the first study on pediatric COVID-19 cases in Vietnam. Due to some changes in the national epidemic strategy to catch up with the actual situation, the screening tests, indications for admission and discharge standards during our study had many changes that followed. However, our study only included the cases really requiring hospitalization for follow-up and treatment.

When compared with adults, children have lower rates of serious illness [16,17]. The proportion of severe or critical illness in children is estimated less than 3% [18,19]. In our study, most cases were mild - moderate condition, consistent with previous reports [20–22]. However, 17.3% of cases progressed to severe/critical level. The proportion is relatively higher than in previous studies, but this can be explained by the fact that our hospital as a tertiary center, admit all the cases that have symptoms or severe comorbidities. Therefore, the rate of severe progression is higher. It is noted that the rate of moderate to severe illness was higher in elder children. The reason for this is that children in older age group are hospitalized only when symptoms of COVID-19 are severe or persistent.

Identifying factors associated with severe disease in pediatric COVID-19 may help primary care physicians to appropriately triage patients for further management. We identified that the proportion of underlying diseases, dyspnea, elevated neutrophile, CRP, ferritin, AST, ALT and D-dimer, consolidation on chest X-rays, all done on admission, in the severe/critical group higher than mild - moderate groups, the differences were statistically significant. Among these factors, underlying disease, dyspnea, elevated CRP >20 mg/L and elevated ferritin were independent factors related to severe illness through multivariable logistic regression analysis.

As with previous studies, comorbidities in children with COVID-19 are a matter of great concern. The children with the history of medical comorbidities (e.g., due to neurologic diseases, developmental delays, or genetic syndromes including trisomy 21), obesity, chronic cardiopulmonary disease, or who are immunocompromised and elder teenagers may be at increased risk of severe disease [11,15]. Our study is not an exception, the rate of children with underlying medical conditions in the severe/critical group at 60%, in which, neurologic diseases, gastrointestinal - hepatic diseases and obesity are the main conditions associated with the risk of severe disease in the children in our study.

In our study, among two groups compared, we noted that neutrophile, CRP and ferritin were statistically significant higher in severe group. Besides, between the moderate group and the severe group, we find that the AST, ALT and D-dimer parameters were higher in the severe group; the difference was statistically significant. Other studies also have shown factors independently associated with severity such as age >10 years, hypoxemia, C-reactive protein level >80 mg/L, elevated IL-6, IL-10 and D-dimer [13,22]. The lung imaging findings in children with COVID-19 were overall less frequent and less severe than in adult patients. Typical lung imaging features of viral respiratory infections in the pediatric population such as increased perihilar markings and hyperinflation were not reported in children with COVID-19 [23–25]. In our study, pulmonary consolidation occurs in 50% of severe/critical cases, which may be due to progressive damage of SARS-CoV-2 infection or further bacterial co-infection. This also contributes to the indication to use antibiotics in clinical practice. The E gene Ct value of the severe group is higher than that of the other two groups. This may explain by the fact that the most severe phase of pediatric COVID-19 is around day 5 to day 7 onwards, and at this stage the viral load has already begun to decrease.

In the early stage of the 4th wave of the COVID-19 pandemic in Vietnam, the treatment of pediatric COVID-19 cases remained inconsistent, with the majority based on adult and foreign guidelines (e.g. WHO, NIH, and so on) [26,27]. The guidelines on anti-inflammatory and anticoagulant therapy for pediatric COVID-19 are still very limited [5, 26–28]. Anti-inflammatory and anticoagulation therapies in the early stage of our study were also carefully considered, however, after the national pediatric COVID-19 protocol was available, these therapies became more widespread [29]. Fortunately, we did not record any cases of serious bleeding complications, only 10 cases had skin bleeding from the injection site. Furthermore, the availability of therapeutic drugs is also an issue. Remdesivir in Vietnam has only been licensed for use in children with COVID-19 since November 9, 2021, so the rate of using remdesivir in moderate to severe group in our study is still low.

The mortality rate will fluctuate across different studies depending on centers, research subjects and the method of sampling. As mentioned above, our hospital is a tertiary care center, admit patients who have symptoms or comorbidities, so the mortality rate in our study is relatively higher than in previous reports [8,12,20]. We also noted that the rate of leukocytosis was higher in the mortality group than in the survival group, the difference was statistically significant. These factors are relatively new and different from factors shown in previous reports such as infants, teenagers, those with cardiac or neurological conditions, or two or more comorbid conditions, and those who are obese [11,15]. This can be explained that the patients who died in the study all had severe comorbidities such as corticoids-resistant nephrotic syndrome, immunodeficiency, neurological disease, and so on (Appendix B), therefore, the possibility of bacterial co-infection is inevitable. In addition, in the fatal group, there was one case had MRSA necrotizing pneumonia and one case had *Stenotrophomonas maltophilia* bacteremia.

4.1. Limitations

Firstly, we were unable to perform diagnostics to identify co-infections, nor their effect on prognosis in this study. Secondly, we did not perform chest CT scan to evaluate lung damage, especially children with lung lesions accompanied with underlying diseases. Finally, our study was a retrospective, single-center study in Vietnam, therefore, this fact makes it difficult to generalize the results of this manuscript to other countries except for Vietnam.

5. Conclusions

In our study, the severe/critical and mortality rates in pediatric COVID-19 cases were relatively high. All fatal cases had severe comorbidities. Underlying disease, dyspnea, elevated inflammatory markers were independent factors related to severity in pediatric COVID-19 cases. More studies are needed to determine the risk factors associated with mortality from COVID-19 in children.

6. ICMJE statement

All authors participated in the study were involved in the treatment and care of the patient. The authors contributed to the writing and agreed to this final manuscript. All authors meet the ICMJE authorship criteria.

Contributor name	The conception and design of the study	Acquisition of data	Analysis and interpretation of data	Drafting the article or revising it critically for important intellectual content	Final approval of the version to be submitted
Phung, N.N.T	X	X	X	X	X
Tran, T.T	X	X	X	X	X
Nguyen, H.T	X			X	X
Le, T.Q	X			X	X
Ngo, M.N.Q	X			X	X
Dang, D.Q		X		X	X
Tran, N.M		X		X	X

(*continued on next page*)

(*continued*)

Contributor name	The conception and design of the study	Acquisition of data	Analysis and interpretation of data	Drafting the article or revising it critically for important intellectual content	Final approval of the version to be submitted
Nguyen, L. B.Y		X		X	X
Tran, T.M		X		X	X
Ngo, G.H.L		X		X	X
Vo, T.T.M		X		X	X

Declaration of competing interest

None declared.

Appendix A. Severity classification based on pediatric COVID-19 guidelines of the Ministry of Health of Vietnam

Severity	Mild	Moderate	Severe	Critical
Characteristics	-Normal respiratory rate for age. -SpO2 $\geq$ 96% in room air.	- Tachypnea for age - SpO_2: 94–95% in room air. - Awake, can eat and drink - Interstitial lesions/the ground glass on chest X-rays.	- Severe pneumonia - SpO_2: 90 - < 94% in room air. - Tired of breastfeeding, eating poorly - Lung lesions $\geq$50% on chest X-rays	- Mechanical ventilation - Cyanosis - SpO_2 < 90% in room air. - Shock - Multi-organ failure. - Cytokine storm.

Appendix B. Characteristics of fatal cases in the study

Case	Age (months)	Comorbidities	COVID-19 severity	Direct cause of death
Case 1	1	Fetal malnutrition Pulmonary hypertension	Critical	Severe pulmonary hypertension
Case 2	72	Sequelae of encephalitis Tracheostomy	Critical	Respiratory failure
Case 3	98	Multiple malformations Atrial septal defect Cerebral palsy Severe anemia	Severe	Severe anemia
Case 4	3	Atrioventricular septal defect Heart failure	Severe	Severe heart failure Pulmonary edema
Case 5	98	Asthma	Critical	Respiratory failure
Case 6	15	Short bowel syndrome Multiple malformations Fungal sepsis	Severe	Severe fungal sepsis
Case 7	89	Cerebral palsy Necrotizing pancreatitis	Critical	Respiratory failure
Case 8	20	Epilepsy Cerebral palsy	Critical	Respiratory failure
Case 9	1	Postoperative of atrophy of small intestine type IIIA	Severe	Sudden cardiac arrest
Case 10	179	Cerebral palsy	Critical	Respiratory failure
Case 11	108	Relapsed nephrotic syndrome	Critical	Respiratory failure
Case 12	2	MRSA necrotizing pneumonia Bilateral pneumothorax Septic shock	Severe	Severe septic shock
Case 13	3	Metabolic disorder	Severe	Severe cerebral edema
Case 14	16	Metabolic disorder	Severe	Severe cerebral edema
Case 15	7	Septic shock	Severe	Severe septic shock
Case 16	7	Cirrhosis Sclerosis cholangitis	Severe	Severe hepatic encephalopathy
Case 17	3	Severe anemia	Severe	Cardiac arrest before admission to hospital
Case 18	119	Myocarditis A-V block degree 3	Severe	Severe cardiogenic shock

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