

## Severe coronavirus disease pneumonia in pediatric patients in a referral hospital

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**Running Head:** Severe respiratory failure in children with COVID-19

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## Abstract

**Objective:** We aimed to evaluate the characteristics and outcomes of critically ill children managed in an intensive care unit because of coronavirus disease (COVID-19) pneumonia with respiratory support requirements.

**Methods:** We performed a single-center retrospective observational study in a pediatric intensive care unit (PICU) with 32 beds in Ankara City Hospital, Ankara, Turkey, from March 13, 2020, to December 31, 2020. Patients who needed positive-pressure ventilation (PPV) therapy for COVID-19 pneumonia were included in the study. Demographic, clinical, and laboratory data were extracted from the patients' electronic medical records. As outcomes, the hospitalization rate of all pediatric patients diagnosed as having with COVID-19 by PCR, PICU admission rate for COVID-19 pneumonia among all hospitalized patients, PPV support rate, intensive care hospitalization duration (days), total hospitalization duration (days), survival rate, and tracheotomy requirement were evaluated.

**Results:** During the study period, 7033 children tested positive for COVID-19 in PCR tests. Of these patients, 1219 were hospitalized for COVID-19. Seventeen patients needed PPV support because of COVID-19 pneumonia. High proportion (65%) of patients admitted to the PICU had co-morbid diseases. Noninvasive ventilation was applied in 15 patients (88%). The hospitalization rate among the children with COVID-19 was 17%, of whom 1.6% were admitted to the PICU. Mortality rates were 0.056% of all the cases and 0.32% of the hospitalized patients in our hospital.

**Conclusion:** The presence of a co-morbid disease could be a sign of severe disease in children with higher lethality. Very few children required PPV support because of severe COVID-19 pneumonia.

## Summary

Coronavirus disease (COVID-19) spread from Wuhan, China, and caused an outbreak that threatened human health globally. Reports worldwide have shown that the outbreak mainly affected the adult population. Data about severe COVID-19 pneumonia in children are limited. Treatment interventions for the adult population have been adapted for children. Our article was aimed at building an opinion about this patient group. We found that severe COVID-19 pneumonia occurred in only a small population. Cardiac and neurological comorbidities are associated with higher mortality rates. Only a few patients with COVID-19 required mechanical ventilation support.

## Severe coronavirus disease pneumonia in pediatric patients in a referral hospital

### 1. INTRODUCTION

Coronavirus disease (COVID-19) spread from Wuhan, China, and caused an outbreak that threatened human health globally within 1 year. As of January 28, 2021, 98,925,221 COVID-19 cases have been documented, including 2,127,294 deaths worldwide [1]. At the beginning of the pandemic, data published about COVID-19 showed that the disease occurred in older patients with co-morbidities and pediatric patients were thought to overcome mild cases of the disease [2]. Fever, cough, sore throat, rhinorrhea, respiratory distress, myalgia, diarrhea, fatigue, and headache are the most common symptoms of COVID-19. Pneumonia (64.9%) was diagnosed in most cases, whereas asymptomatic infection was less common (15.8%) [3]. Reports from China showed that 90% of pediatric patients with COVID-19 had mild-to-moderate disease [4]. Garcio-Solido et al. [5] showed that of 512 children with COVID-19 disease or suspected new coronavirus infection, only 11, including 7 with confirmed COVID-19, needed intensive care.

The respiratory support requirement in critically ill children with COVID-19 varies across reports, and reports about pediatric positive-pressure ventilation (PPV) in COVID-19 patients are lacking. According to a study from the United States, 40 of 70 critically ill patients required invasive mechanical ventilation (IMV) [6]. In another study, Oualha et al. [7] showed that 9 of 20 patients with COVID-19 admitted in the PICU needed invasive respiratory support.

The main objective of our study was to examine the incidence, implementation, and results of noninvasive and invasive PPV support therapies in patients in a pediatric intensive care unit (PICU) of a tertiary referral hospital.

## 2. MATERIALS AND METHODS

### 2.1. Study design

We conducted a single-center retrospective observational study in pediatric patients with COVID-19 who needed noninvasive (NIV) or IMV in a tertiary referral hospital that has been identified as a regional reference center in Ankara City Hospital, Ankara, Turkey, for children with COVID-19. The medical records of the patients who attended the hospital between March 13, 2020, and December 31, 2020, were reviewed. COVID-19 was diagnosed by a real-time polymerase chain reaction (RT-PCR) test using nasopharyngeal and lower respiratory tract secretions. Severe COVID-19 pneumonia was defined as fever, tachypnea, and hypoxia (oxygen saturation [ $SpO_2$ ] < 90% in room air). Polymerase chain reaction tests were performed in the emergency service in the referral hospital. None of the patients had remote COVID-19 or multiple inflammatory syndrome. Patients who needed PPV therapy for COVID-19 pneumonia were included in the study. Patients who did not require PPV for COVID-19 pneumonia were excluded from the study.

### 2.2. Data collection

Demographic, clinical, and laboratory data were extracted from the patients' electronic medical records. The patients' respiratory support requirement before PICU admission, symptoms (cough, diarrhea, dyspnea, fever, headache, impairment of smell and taste, nausea, rhinorrhea, and vomiting), vital signs (peripheral oxygen saturation, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure),  $SpO_2$ -to-fraction of inspired oxygen ( $FiO_2$ ) ratio, pediatric risk of mortality (PRISM-III) score, pediatric sequential organ failure assessment (pSOFA) score, laboratory tests (hemogram, C-reactive protein, ferritin, interleukin6, procalcitonin, venous blood gas analyses, pro-brain natriuretic peptide, troponin-

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3 I, and liver and kidney function tests), and imaging tests (chest computed tomography) at  
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5 PICU admission were recorded. Pharmacological treatments (antibiotherapy, antiviral  
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7 therapy, intravenous immunoglobulin, systemic steroids, inotropic agents, and low-molecular-  
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9 weight heparin therapy) and respiratory support treatments (high-flow nasal cannula [HFNC]  
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11 treatment, and NIV and IMV) given during hospitalization in the PICU were investigated.  
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### 15 **2.3. Outcomes**

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18 The outcomes evaluated included the hospitalization rate among all pediatric diagnosed as  
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20 having COVID-19 by PCR, PICU admission rate for COVID-19 pneumonia among all  
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22 hospitalized patients, PPV support rate, intensive care hospitalization duration (days), total  
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24 hospitalization duration (days), survival rate, and tracheotomy requirement.  
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### 28 **2.4. Statistical analysis**

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31 A descriptive analysis of the results was performed using the SPSS 17.0 software package for  
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33 Windows (IBM Company, New York, NY). Descriptive statistics were used for all study  
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35 variables. Categorical data were expressed as proportions (%). Medians and interquartile  
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37 ranges were used for quantitative data.  
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### 41 **2.5. Ethics committee approval**

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44 Ethics committee approval was received for this study from the ethics committee of Ankara  
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46 City Hospital (November 25, 2020; E1-20-1296).  
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## 49 **3. RESULTS**

### 50 **3.1. Demographic data and pre-intensive care parameters**

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53 The study was conducted from March 13, 2020, to December 31, 2020. During the study  
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55 period, 7033 children who presented to the pediatric emergency service were diagnosed as  
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57 having COVID-19 by PCR test. After examination, patients who needed hospitalization were  
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3 transferred to the ward. A total of 1,219 patients (17.3% of all patients with COVID-19) were  
4 hospitalized for COVID-19. Twenty patients (1.6% of all hospitalized patients with COVID-  
5 19) required PICU admission for COVID-19 pneumonia. All the patients who were admitted  
6 to the PICU had hypoxia and pediatric acute respiratory distress syndrome. All the  
7 patients' SpO<sub>2</sub>/FiO<sub>2</sub> ratios were <264. Seventeen patients with COVID-19 pneumonia who  
8 received PPV support were included in the study.  
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11 The median age of the patients was 96 months (interquartile range [IQR], 11.5–182.5  
12 months). Male patients were predominant (58%). Most patients (65%) had a co-morbid  
13 disease. The median PRISM-III and pSOFA scores were 7 (IQR, 7–9) and 4 (IQR, 4–6),  
14 respectively. All the patients had cough and dyspnea. Thirteen patients (76%) had a fever.  
15 Diarrhea was found in 1 patient. Septic shock occurred in 1 patient. Generalized  
16 maculopapular rash was found in 1 patient. Three patients required respiratory support before  
17 intensive care admission, of whom one was intubated at the reference hospital. One of the  
18 patients underwent tracheotomy with home-type mechanical ventilation support before PICU  
19 admission because of chronic respiratory failure. Another patient received high-flow oxygen  
20 therapy at the ward. The median SpO<sub>2</sub>/FiO<sub>2</sub> ratio was 138 (IQR, 99.5–197). The patients'  
21 demographics and clinical features at admission are shown in Table 1.  
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### 44 **3.2. PICU follow-up**

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46 Laboratory parameters and radiological findings are presented in Table 2. Most patients  
47 (82.4%) had lymphopenia. In most patients, the values of the inflammatory parameters (C-  
48 reactive protein, ferritin, IL-6, and pro-calcitonin) and pro-brain natriuretic peptide levels  
49 were high. Chest computed tomography (CT) was performed in all the patients because all  
50 had severe pneumonia that required PPV support. In radiological examinations, nearly all the  
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3 patients had ground-glass opacity (GGO;96.4%). Other common CT findings were  
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5 parenchymal infiltration (76.4%), pleural effusion (47.1%), and bronchial thickening (23%).  
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9 The respiratory support treatments applied in the patients are presented in Table3. The median  
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11 duration of IMV was 11 days (IQR, 2.5–27.5 days). The median NIV duration was 4 days  
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13 (IQR,2–6 days). Bi-level positive airway pressure (BPAP) mode was preferred in all the  
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15 patients who underwent NIV. When we examined all the patients admitted to the PICU, we  
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17 found that NIV was applied in 15 patients and IMV was applied in 10 patients. Pneumothorax  
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19 and pneumomediastinum were found in 1 patient who received IMV. We did not find any  
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21 other complications in the patients who received NIV/IMV. Five patients (29.4%) required  
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23 inotropic therapy during follow-up. The medicines administered were favipiravir (n=9),  
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25 systemic steroid (n=7), chloroquine (n=6), low-molecular-weight heparin (n=6), intravenous  
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27 immunoglobulin (n=3), azithromycin (n=2, and lopinavir/ritonavir (n=1; Table3).Renal  
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29 replacement therapy or plasmapheresis was not necessary for any patients. Prone position and  
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31 high-frequency oscillatory ventilation (HFO) were applied in 1 patient, who required  
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33 extracorporeal membrane oxygenation (ECMO) support. ECMO cannulation was performed  
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35 in our hospital before the patient was transferred to another hospital.  
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## 41 **Outcomes**

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44 The hospitalization rate of all the pediatric patients diagnosed as having COVID-19 by PCR  
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46 test was 17.3%. The PICU admission rate was 1.64% of all the hospitalized patients. The PPV  
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48 support rate was 1.39%. The mortality rates were 0.056% of all cases and0.328% of the  
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50 hospitalized patients in our hospital. The lethality rate was 23.5% in the patients managed in  
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52 the PICU. The median PICU stay duration was 7 days (IQR, 6.0–18.5 days). The median  
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54 length of hospital stay was 16.5 days (IQR, 9.5–44.5 days). Thirteen patients survived  
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56 (76.5%), and 4 patients died. Three patients were male, and 1 patient was female in non-  
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3 survivor group. One male patient was a six-month-old infant who had transposition of the  
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5 great arteries. Two of non-survivors were school-age children, and the remaining patient was  
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7 an adolescent. Another 11-year-old male non-survivor also had pulmonary hypertension and  
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9 Down syndrome. A female non-survivor patient underwent stem cell transplantation and had  
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11 chronic lung disease. One of the school-age patients who died had no co-morbid disease and  
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13 received ECMO for 19 days. Tracheotomy was applied in 2 patients because of weaning  
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15 failure from mechanical ventilation, of whom one survived.  
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#### 23 **4. DISCUSSION**

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26 This report describes a single-center study in children who were critically ill owing to  
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28 COVID-19 pneumonia. Most children in our study who were admitted to the PICU had  
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30 neurological or cardiac co-morbid diseases. The hospitalization rate was 17.3%, and 1.6% of  
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32 the patients in our cohort were admitted to the PICU. The hospitalization rate was unusually  
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34 large. This was a result of the recommendation of our National Health Guide for pediatric  
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36 patients with COVID-19 to control the pandemic in the first 6 months from onset [8]. Our  
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38 national guide suggests that all symptomatic patients, patients with co-morbidities, those with  
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40 pneumonia independent of age, those with fever for >24 hours, and those with organ  
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42 involvement in COVID-19 [8]. Reports from the United States at the beginning of the  
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44 pandemic showed that the estimated hospitalization rate differed from 6% to 20%, and  
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46 0.58%–2% of the patients were admitted to the PICU [9]. When the virus became endemic in  
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48 the United States in March 2020, 20% of the patients were hospitalized and 10% were admitted  
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50 to the ICU. Three patients died (0.4% of all cases and 2% of those admitted). [10] A report  
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52 from Europe showed an 8% PICU admission rate [6].  
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3 In our patient group, the mortality rates were 0.056% of all the cases and 0.328% of all  
4 hospitalized patients. The PPV support requirement was too low (1.39%) in all the  
5 hospitalized patients. The hospitalization and PICU admission rates were similar to other  
6 reports. The mortality rate and PPV support requirement in our cohort differed from other  
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15 Shekerdemian et al.[11] declared that 56% of children followed up in the United States and  
16 Canada PICU belonged to the adolescent age group. Less than 1% of the children with  
17 COVID-19 were <10 years of age in the review of the Chinese Center for Disease Control and  
18 Prevention [9]. Most of our patients who were managed in the PICU were infants and  
19 adolescents.  
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28 Although children are prone to developing acute respiratory disease syndrome, COVID-19  
29 causes milder forms of the disease in pediatric patients [12]. This may be related to the host  
30 and disease exposure or other unknown factors. The theories about this condition include the  
31 difference in immune system between children and adults. Another theory is the difference in  
32 angiotensin-converting enzyme receptor expression [13].  
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41 Adult patients with COVID-19 who have underlying diseases such as hypertension, diabetes,  
42 or cardiovascular diseases have more severe diseases than other patients [14]. Most pediatric  
43 patients with COVID-19 admitted to the PICU have co-morbid diseases[6,7]. Sixty-five  
44 percent of our patients had a co-morbid disease.  
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51 Like the clinical features of other respiratory viruses, those of COVID-19 range from  
52 asymptomatic infection to severe pneumonia with respiratory failure [10]. Cough and dyspnea  
53 were the symptoms found in our patients at admission. Fever, diarrhea, shock, and rash were  
54 also found. Adult symptoms such as impairment of smell and taste, dizziness, and headache  
55 were not observed. Generalized erythematous rash was found in 1 patient.  
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3 Chest CT is one of the main diagnostic tools for COVID-19 pneumonia in adult patients. The  
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5 CT imaging findings of COVID-19 pneumonia are atypical, with more localized GGO extent,  
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7 lower GGO attenuation, and relatively rare interlobular septal thickening [15]. Similarly to  
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9 those in other studies, GGO and parenchymal infiltration were the most common CT findings  
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11 in our patients.  
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15 Lymphopenia was found in nearly all our pediatric patients like in adult patients with  
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17 COVID-19. In adult studies, lymphocytopenia occurred in most patients [16, 17]. However,  
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19 reports about children hospitalized for COVID-19 showed that lymphopenia occurred in a  
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21 small percentage of patients and was not related to severe disease [17, 18]. This situation may  
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23 be correlated with the characteristics of our population. We need more clinical information or  
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25 studies to explain this result. The values of the inflammatory parameters and pro-BNP levels  
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27 were high in our patients. We did not find any abnormalities in the other laboratory  
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29 parameters.  
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34 The median IMV support duration at the beginning of the pandemic was 10 days [11]. A  
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36 relatively large study from New York City reported a median IMV duration of 6.7 days.[6]  
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38 The median IMV support duration in our study was 11 days. This may be related to factors  
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40 such as disease severity, genetics, or environmental differences. NIV support use was  
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42 relatively low in other studies [6, 11]. We used NIV as BPAP support at admission or after  
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44 extubation in 88% of the patients in negative-pressure chambers. Few recommendations were  
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46 made for the application of respiratory support devices in children at the beginning of the  
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48 pandemic. Pediatric guidelines recommend that children with severe respiratory distress  
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50 should be supplied with oxygen therapy when their oxygen saturation level is <90%. If  
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52 hypoxia remains, oxygen support should be escalated to HFNC or NIV. In children with  
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54 COVID-19 respiratory failure, NIV should be escalated to IMV [19, 20]. Our intensive care  
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56 team applied this medical treatment protocol to our patients successfully. Respiratory support  
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3 therapies should be considered step-by-step in pediatric patients with COVID-19 pneumonia.  
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5 Early intubation should not be performed if IMV support is not necessary. Of course,  
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7 respiratory support therapies should be applied in negative-pressure chambers by clinicians  
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9 with appropriate education, using appropriate equipment [19, 20]. We isolated our patients in  
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11 single negative chamber rooms. We had enough personal protective equipment for  
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13 interventions and patient care. We did not find any hospital-acquired COVID-19 cases in our  
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15 health care staff.  
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20 One of our patients had tracheotomy with home-type mechanical ventilation support before  
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22 PICU admission because of chronic respiratory failure. In the patient, COVID-19 pneumonia  
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24 did not result in chronic respiratory failure, as the patient already had chronic respiratory  
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26 failure. Tracheotomy was applied in 2 patients because of weaning failure from mechanical  
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28 ventilation. Both patients had co-morbid diseases. One of them already received BPAP  
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30 support therapy at home. Thus, tracheotomy was not used as a specific therapy for COVID-19  
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32 management in pediatric patients.  
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37 In our study, the mortality rate was higher than that in other pediatric studies. This may be a  
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39 result of the exclusion of patients with COVID-19 who did not receive respiratory support and  
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41 those with mild and moderate COVID-19 pneumonia. Fatal outcome was observed in 4  
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43 patients. Three of them had at least 2 co-morbidities. Two patients had complex cardiac  
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45 malformations, and one had a bone marrow transplant and chronic lung disease. Only one  
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47 patient who had no co-morbidity died. All the patients who survived were discharged from the  
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49 hospital 28 days after admission.  
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54 This study has several limitations. This study was a single-center retrospective study and did  
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56 not include any control group for comparison. Our results cannot be generalized to all  
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58 pediatric populations because of the small sample size. We could not classify pediatric acute  
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3 respiratory distress syndrome according to oxygenation index or oxygen saturation index  
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5 because of missing ventilatory pressure values. The medical treatments applied were not  
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7 standardized for all the patients. The medicines used for the pediatric patients with COVID-19  
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9 were decided by pediatric infectious disease specialists with the guidance of the advisory  
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11 committee constituted by the Ministry of Health. Furthermore, larger multicenter studies are  
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13 needed to define the incidence, risk factors, and development of critical illness in children  
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15 with COVID-19.  
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20 In conclusion, this paper describes critically ill pediatric patients with COVID-19 who  
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22 required PPV. Like other studies published worldwide, this study shows that a small pediatric  
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24 population required intensive care and mechanical ventilatory support. Infant and adolescent  
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26 age groups require more respiratory support than other age groups. Lymphopenia, high levels  
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28 of inflammatory markers, and high pro-BNP levels were found in the critically ill pediatric  
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30 patients with COVID-19 in this study. NIV can be safely used in negative-pressure chambers.  
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33 All health care workers should be aware of the intensive care requirement in pediatric patients  
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35 with COVID-19 who have co-morbid diseases (especially neurological and cardiac diseases).  
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**Table 1.** Demographics and clinical features of patients, n=17

	Value
<b>Age in months, median (IQR)</b>	96 (11.5-182.5)
<b>Age in groups, n (%)</b>	
Infant	6 (35)
Preschool age	1 (6)
School age	3 (17)
Adolescent	7 (41)
<b>Sex, n (%)</b>	
Male	10 (58)
Female	7 (42)
<b>Co morbid Disease, n (%)</b>	11 (65)
Neurological	7
Cardiac	4
Respiratory	2
Genetic	2
Stem Cell Transplant	1
<b>PRISM-III score, median</b>	7 (7-9)
<b>pSOFA score, median</b>	4 (4-6)
<b>Vital signs at admission to PICU</b>	
Temp. °C, median (IQR)	36.7 (36.4-37.7)
Heart rate, bpm, median (IQR)	125 (117.5-152)
SBP, mmHg, median (IQR)	101 (114-117.5)
DBP, mmHg, median (IQR)	63 (52.5-67.5)
RR, bpm, median (IQR)	34 (31-42)
SpO <sub>2</sub> percentage, median (IQR)	99 (96-100)
SpO <sub>2</sub> /FiO <sub>2</sub> ratio, median (IQR)	138 (99.5-197)
<b>Presenting symptoms at admission to PICU, n (%)</b>	
Cough	17 (100)
Dyspnea	17 (100)
Fever	13 (76)
Diarrhea	1 (6)
Shock	1 (6)
Rash	1 (6)

Bpm, breaths per minute; DBP, diastolic blood pressure; IQR, inter quartile range; RR, respiratory rate; SBP, systolic blood pressure; SpO<sub>2</sub>, peripheral oxygen saturation; PICU, pediatric intensive care; PRISM, Pediatric Risk of Mortality; pSOFA, Pediatric Sequential Organ Failure Assessment.



**Table 2.** Radiological findings and laboratory results at admission to PICU, n=17

	Value
<b>Abnormalities on chest CT, n (%)</b>	
Ground-glass opacity	16(94)
Parenchymal infiltration	13(76)
Pleural effusion	8(47)
Bronchial thickening	4(23)
Air leak	1(6)
<b>Laboratory findings. median (IQR)</b>	
Venous pH {n=17}	7.40(7.26-7.46)
Venous pCO <sub>2</sub> , mm Hg {n=17}	39.8(34.0-49.9)
Venous HCO <sub>3</sub> , mmol/L {n=17}	22.4(20.7-26.1)
Venous Lactate, mmol/L {n=17}	1.75(1.30-3.04)
WBC, per mm <sup>3</sup> {n=17}	8960(6095-11360)
Absolute lymphocyte count. per mm <sup>3</sup> {n=17}	880(630-2420)
Hemoglobin, g/dl {n=17}	12.4(9.7-13.4)
Platelets, per mm <sup>3</sup> {n=17}	306(170-401)
CRP, mg/dl {n=17}	29(9.5-99.50)
D-Dimer, mg/L {n=17}	1.52(0.36-4.89)
BUN, mg/dl {n=17}	19(14-33)
Creatinine, mg/dl {n=17}	0.36(0.25-0.70)
AST, U/L {n=17}	45(26-62)
ALT, U/L {n=17}	36(19-80)
LDH, U/L {n=17}	419(344-556)
Total bilirubin, mg/dl {n=17}	0.30(0.25-0.50)
Troponin-I, ng/L {n=15}	4(2.5-11)
pro-BNP, ng/L {n=14}	495.5(182-2617)
Procalcitonin, µg/L {n=13}	0.28(0.16-0.77)
Ferritin, µg/L {n=8}	224.5(70.7-325.2)
IL-6, pg/ml {n=7}	66.20(6.88-307)

ALT, alanine amino transferase; AST, aspartate amino transferase; pro-BNP, pro-B type natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; CT, computerized tomography; IL, interleukin; IQR, inter quartile range; LDH, Lactate dehydrogenase; PICU, pediatric intensive care unit; WBC, white blood cell count.

**Table-3.** Treatments administered to patients and outcomes, n=17

	Value
<b>Respiratory support, n (%)</b>	
NIV→Mask Oxygen	5 (29.4)
IMV→NIV→Mask Oxygen	4 (23.4)
NIV→IMV	3 (17.6)
NIV→HFNC	2 (11.7)
IMV	2 (11.7)
NIV→IMV→HFNC	1 (5.8)
<b>Days on respiratory support, median (IQR)</b>	
NIV	4(2-6)
IMV	11(2.5-27.5)
<b>Medical treatment, n (%)</b>	
Favipiravir	9(53)
Systemic Steroid	7(41)
Chloroquine	6(35)
LMWH	6(35)
IVIG	3(17)
Azithromycin	2(12)
Lopinavir/ritonavir	1(6)
Inotropic agents	5 (29)
<b>Days on PICU, median (IQR)</b>	7(6-18.5)
<b>Days on hospital, median (IQR)</b>	16.5(9.5-44.5)
<b>Survival, n (%)</b>	13(76)
<b>Tracheotomy requirement, n (%)</b>	2(12)

IMV, invasive mechanical ventilation; IQR, inter quartile range; IVIG, intravenous immune globulin; HFNC, high flow nasal cannula therapy; NIV, non-invasive mechanical ventilation; LMWH, low molecular weight heparin; PICU, pediatric intensive care unit