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ORIGINAL ARTICLE
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Clinical Characteristics and Treatment of COVID-19 Patients Admitted to the Pediatric Intensive Care Unit in Our Center

Hastanemiz Çocuk Yoğun Bakım Ünitesine Kabul Edilen COVID-19 Hastalarının Klinik Özellikleri ve Tedavileri

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ABSTRACT

Aim: The aim of this study was to evaluate the clinical and laboratory features and to determine the treatment options of COVID-19 patients hospitalized in the Pediatric Intensive Care Unit.

Material and Method: We retrospectively reviewed the patients who were diagnosed with COVID-19 and admitted to the pediatric intensive care unit (PICU) with 32 beds in Ankara City Hospital between March 16, 2020 and December 16, 2021. Patient characteristics included age, gender, contact history, and co-morbidities. Laboratory investigations included complete blood count, biochemical evaluations, chest X-ray, and computed tomographic imaging of the thorax. Respiratory support therapy, extracorporeal therapy, and other medical treatments were recorded.

Results: A total of 82 patients were admitted to the PICU after being diagnosed with COVID-19. Of all patients 64.6% (n=53) were male. The median age of the patients was 126.5 (37-185) months. Nearly half of the patients had a SpO_2 below 92%. About half of the patients had lymphopenia, anemia, and elevated CRP and D-Dimer levels. Of the patients, 60% (n=47) were supported with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC) oxygen therapy, whereas 35% (n=28) were followed on invasive mechanical ventilation. The length of stay in the PICU was 11 days, whereas the total length of stay in the hospital was 19 days. Twelve patients (15.2%) died.

Conclusion: In line with previous studies, our study planned to contribute to the literature in order to fill the diagnostic gap through clinical findings, laboratory values and chest radiographic examinations in COVID-19.

Keywords: COVID-19, pediatrics, pediatric intensive care unit, respiratory support methods, critical patient.

ÖZ

Amaç: Bu çalışmanın amacı Çocuk Yoğun Bakım Ünitesine yatan COVID-19 hastaların klinik ve laboratuvar bulgularını değerlendirmek ve tedavi seçeneklerini saptamaktı.

Gereç ve Yöntem: Otuz iki yataklı Ankara şehir Hastanesi çocuk yoğun bakım ünitesine (ÇYBÜ) kabul edilen hastalardan 16 Mart 2020 ile 16 Aralık 2021 tarihleri arasında COVID-19 tanısı almış hastalar retrospektif olarak tarandı. Vakalar yaş, cisiyet, temas hikayesi, eşlik eden hastalıklar ve karakteristik bulgular olarak tarandı. Laboratuvar parametreleri olarak tam kan sayımı, rütin biyokimya, akciğer grafisi, toraks bigisayarlı tomografi ile değerlendirildi. Solunum destek tedavisi ve ekstrakorporyal tedavi, medikal tedaviler kaydedildi.

Bulgular: COVID-19 tanısı alıp ÇYBÜ' ye kabul edilen hasta sayısı 82'ydi. Hastaların %64,6'sı (n=53) erkekti. Hastaların median yaşı 126,5 (37-185) aydı. Hastaların yaklaşık yarısının SpO_2 değeri %92'nin altında idi. Hastaların yaklaşık %50'sinde lenfopeni, anemi, CRP ve D-Dimer yüksekliği görüldü. Hastaların %60'ının (n:47) noninvaziv mekanik ventilasyon (NIV) veya yüksek akımlı nazal oksijen tedavisi (HFNC), desteğine ihtiyacı varken, %35'si (n:28) invaziv mekanik ventilatörde izlendi. ÇYBÜ'de kalış süresi 11 gün, hastanede kalış süresi ise 19 gündü. On iki hasta (%15.2) kaybedildi.

Sonuç: Literatür verilerinin ışığında, Çocuk yoğun bakım ihtiyacı gösteren ağır COVD-19 olgularının klinik semptomları labotavuar verileri ve toraks görüntülemelerinde sıkça karşılaşılan tanısal eksiklikleri gidermek ve literatüra dikkati çekmektir.

Anahtar Kelimeler: COVID-19, pediatrik, çocuk yoğun bakım ünitesi, solunum destek uygulama yöntemleri, kritik hasta.

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INTRODUCTION

COVID-19 is a disease caused by severe acute respiratory syndrome Coronavirus type-2, which emerged in Wuhan, China at the end of 2019 and continues to spread all over the world (1). The World Health Organization (WHO) reported that, as of 03 December 2021, COVID-19 has been detected in more than 260 million people worldwide, resulting in the death of approximately 5 million people, and a total of 7.8 million doses of COVID-19 vaccines administered. According to the World Health Organization, the average worldwide mortality rate is 2.2% (2). Although COVID-19 usually has an asymptomatic course in infected individuals, 10-15% of them receive oxygen therapy in intensive care units and 5% need mechanical ventilatory support (3). SARS-CoV-2 was initially thought to involve only the respiratory system and cause death due to ARDS. However, as a result of the pandemic in Europe and America, it has been understood that COVID-19 causes involvement in the gastrointestinal, cutaneous and neurological systems, and finally, multisystemic inflammatory syndrome (MIS) (4). It has been reported that all these involvements lead to critical diseases and eventually cause death. Mortality rates differ between countries. Most COVID-19 patients have a mild or asymptomatic disease course. Serious (2.1%) or critical (1.2%) disease was reported in only a small portion of the patients (5). The direct identification of viral RNA in nasopharyngeal swab samples by real-time polymerase chain reaction is the most commonly used diagnostic method for COVID-19. It has been described that this method can detect viral RNA in nasopharyngeal, bronchoalveolar and stool samples (6).

In our single-center study, we investigated the diagnostic methods, course and management of the disease and the need for medical and respiratory support in patients hospitalized in pediatric intensive care units due to SARS-CoV-2 during the COVID-19 pandemic in our country.

MATERIAL AND METHOD

Our study had a single-center retrospective study design. This study included patients aged 1 month to 18 years diagnosed with COVID-19 based on PCR testing for SARS-CoV-2 and admitted to the pediatric intensive care unit (PICU) with 32 beds in Ankara City Hospital between March 16, 2020 and December 16, 2021. All patients with suspicious or negative PCR results for SARS-CoV-2 were excluded from the study.

All children with a confirmed SARS-CoV-2 infection in nasopharyngeal swab samples by quantitative RT-PCR were included in the study. SARS-CoV-2 was identified by the method targeting the RNA-dependent RNA polymerase (RdRp) gene using the Bio-Speedy COVID-19 RT-qPCR Detection Kit (Bioeksen, Istanbul, Turkey). Using this method, at least one positive test result was considered significant.

Demographic data, comorbidities, symptoms at admission, indications for PICU admission, and physical examination findings (whole body and neurological, respiratory and circulatory system findings) were recorded on a joint study form. Laboratory examinations at admission, including complete blood count (total lymphocyte count, absolute lymphocyte count, hemoglobin level, platelet count), coagulation parameters (PT, aPTT, INR, fibrinogen, D-dimer), C-reactive protein (CRP), procalcitonin, troponin I/T, brain natriuretic peptide (BNP), and ferritin levels were recorded. Laboratory values outside the normal reference ranges were determined.

Antibiotic and antiviral drugs given to the patients were recorded. The respiratory support methods [high flow nasal oxygen therapy (HFNC), non-invasive and invasive mechanical ventilation] applied were determined. The Complications at baseline and during the follow-up were recorded.

Organ dysfunctions were classified into respiratory, circulatory, neurological, renal, hepatic, and hematological types, where 2 or more acute organ failures were defined as multiple organ dysfunction syndrome (MODS) (7). Types of extracorporeal therapies [renal replacement therapies (RRT), total plasma exchange (TPE) and extracorporeal membrane oxygenation (ECMO)] were recorded.

The Length of stay in the intensive care unit and respiratory and/or neurological sequelae at discharge from the ICU were recorded. The mortality rates in the groups and the main factors affecting the mortality rates were determined.

This study was carried out with the permission of the Ministry of Health dated 14 May 2020 (Ethics committee 20-567) and the approval of the local ethics committee (Ethics committee number: 567).

Statistical analysis

Data were analyzed using (Statistical) Package for the Social Sciences (IBM SPSS Statistics, IBM Corporation). Normality distribution of numerical data was evaluated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test). Descriptive statistics included median, range [interquartile range (IQR)], mean, standard deviation, number, and percentage. Comparisons of categorical variables were performed using the Chi-square test. Comparisons of laboratory values between the two groups were made using the independent samples t-test or the Mann-Whitney U test depending on the normality of the distribution. The significance level was set as $p < 0.05$.

RESULTS

The result of the COVID-19 test was positive in 3.4% (n=82) of 2445 patients admitted to the PICU with different diagnosis. In our study, patients hospitalized in the PICU due to COVID-19 were examined. The median age of COVID-19 positive patients was 126.5 (37-185) months, and the 64.6% (n=53) were male. Nine (11%) of the patients were refugee and 30 (36.6%) had a history of contact with COVID-19.

The most common symptoms at the time of admission to the PICU were respiratory distress (64.2%), fever (53.7%) and cough (52.4%). On physical examination, the most common pathological findings in respiratory system examination were rales (56.8%) and rhonchi (53.1%), respectively. The most common comorbidities were neurological diseases [epileptic diseases (36.3%) and cerebral palsy (31.7%)]. In addition, metabolic and respiratory diseases were other common comorbidities. There were 40 (49.4%) patients with an SpO_2 below 92% and 23 (28.7%) patients with an FiO_2 above 60, which were considered criteria for having hypoxia. Demographic and clinical findings of the patients are shown in **Table 1**.

Table 1. Demographic and clinical characteristics of patients infected with COVID-19

Parameter	Number (%)
Demographic characteristics	N: 82
Age (month), median (IQR)	126.5 (37-185)
Refugee	9 (11)
Male (%)	53 (64.6)
Severity of the disease	
PRISMIII score (median)	30 (25-35)
PELOD2 score (median)	25 (21-31)
OSI (median)	11 (0-15.5)
FiO_2(median)	23 (28.7)
Clinical characteristics	
Contact history	30 (36.6)
Comorbidity	39 (54.1)
Cough	43 (52.4)
Fever	44 (53.7)
Shortness of breath	52 (64.2)
SaO_2 <92%	40 (49.4)
Crackles	46 (56.8)
Rhonchi	43 (53.1)
Respiratory Failure	62 (78.5)
Circulatory Failure	33 (41.8)
Other Failure (Neurological, Renal, Hematological, Hepatic)	29 (36.7)

IQR: Inter quartile range, Pediatric Risk of Mortality Score (PRISMIII), Pediatric Logistic Organ Dysfunction (PELOD2), Oxygen saturation in arterial blood (SaO_2), OSI: Oxygen Saturation Index, FiO_2: Fraction of Inspired Oxygen

Patients admitted to the PICU had low lymphocyte counts, hemoglobin and thrombocyte levels (65.4%, 48.1%, 27.2%, respectively). There were high levels of C-reactive protein, pro-brain natriuretic peptide and D-Dimer (68.4%, 40%, 51.5%, respectively). The laboratory values of the patients are shown in **Table 2**.

Table 2. Laboratory Values and radiological findings of patients with COVID-19

Parameter and Tests	
Laboratory Values	**N (%)**
Mean WBC/mm3	7200
Neutropenia (<1500/mm3)	25 (30.5)
Mean Lymphocyte count /mm3	1185
Lymphopenia (<1500/mm3)	53 (65.4)
Anemia	39 (48.1)
Thrombocytopenia (<150000/mm3)	22 (27.2)
Elevated CRP	54 (68.4)
Mean procalcitonin level ±SD	55.10 ±35.1
Elevated Procalcitonin	21(40)
Mean ferritin levels ±SD	1802.14 ±12120
Elevated Ferritin	16(35)
Mean D-Dimer levels	1005.52 ±1291.06
Elevated D- dimer	35 (51.5)
Elevated PT	8 (11.4)
Elevated aPTT	18 (25.4)
BNP	33 (40)
Radiological findings	
Chest-X-Ray	
Bilateral peribronchial thickening and/or peripheral opacities	7 (9)
Multifocal or diffuse GGOs and/or consolidation without specific distribution	12 (14.6)
No findings	42 (51.4)
CT	
Multifocal or diffuse GGOs and/or consolidation without specific distribution	17 (34.2)
Bilateral peripheral and/or subpleural GGOs and/or consolidation lower lobe predominant pattern	8 (18.6)
No findings	12 (25.1)

WBC: White blood cell, CRP: C-reactive protein, SD: standart deviation, PT: prothrombin time, Aptt: activated partial thromboplastin time, CT: computed tomography, GGOs: Ground-Glass Opacities

The radiological findings of the patients were as follows. Half of the radiographic examinations (51.4%, n=42) revealed normal results. Multifocal or diffuse ground-glass infiltration and/or consolidations were the most common (14.6%, n=12) pathological findings on chest X-Ray. Multifocal or diffuse ground glass opacities (GGOs) and/or consolidation without specific distribution was seen in 17 (34%) and bilateral peripheral and/or subpleural GGOs and/or consolidation lower lobe predominant pattern was seen in 8 (18,6%) patients on thoracic CT imaging. The radiological findings are shown in **Table 2**.

Our patients had almost equal rates of need for HFNC and NIV support (59.5%). There were 28 (35.4%) patients who did not benefit from these supportive treatments or who were intubated and received invasive mechanical ventilatory support. Of these patients, 4 (5.1%) had to undergo tracheostomy tube placement.

Antibiotic treatment was commenced for almost all of the patients (97.5%) admitted to the PICU. The more frequent (58.2%) use of favipiravir initially was preferred

to the more frequent (73.4%) use of methyl prednisolone later on. Two patients underwent plasmapheresis due to multiple organ dysfunction syndrome. Renal replacement therapy was performed in five patients with fluid overload that did not improve with volume resuscitation. Veno-venous ECMO (VV-ECMO) as performed in one patient due to high inotrope score and multiple organ dysfunction syndrome. This patient died 1 month later. 'The therapy modalities and patient outcome are presented at Table 3.

Table 3. Therapy modalities and patient outcome

Therapy modalities and patient outcome	N (%)
Oxygen therapy	61 (77.2)
HFNC	47 (59.5)
NIV/CPAP/BIPAP	47 (59.5)
Conventional MV	28 (35.4)
HFO	1 (1.3)
Need for tracheostomy	4 (5.1)
Antiviral therapy	50 (63.3)
Antibacterial therapy	77 (97.5)
Antifungal therapy	10 (12.8)
IVIG	14 (17.7)
Steroid	58 (73.4)
Inotrope	28 (35.4)
Hydroxychloroquine	7 (8.9)
Azithromycin	4 (5.1)
Favipiravir	46 (58.2)
Lopinavir/ritonavir	3 (3.8)
Immunoplasma	6 (7.6)
LMWH	48 (60.8)
RRT	5 (6.3)
Plasmapheresis	2 (2.5)
ECMO	1 (1.3)
Stay of length in PICU, day, median (IQR)	6.5 (3-12)
Stay of length in hospital, day, median (IQR)	14.5 (7.5-23)
Discharge	53 (67.1)
Mortality Rate	12 (15.2)

HFNC:High Flow Nasal Cannula, NIV/CPAP/BIPAP: Non-Invasive Ventilation/Continuous Positive Airway Pressure/Bilevel Positive Airway Pressure, MV: Mechanical Ventilation, HFO: High-Frequency Oscillation, IVIG: Intravenous Immuno Globulin, LMWH:Low-Molecular-Weight Heparin, RRT: Renal Replacement Therapy, ECMO:Extra Corporeal Membrane Oxygenation, PICU: Pediatric Intensive Care Unit, Antiviral Therapy*: Oseltamivir, Immunoplasma*: Convalescent Plasma Therapy.

The length of stay in the PICU was 6,5 (3-12) whereas the total length of stay in the hospital was 19 days 14,5 (7,5-23). Twelve patients (15.2%) died, but 5 patients recovered with sequelae.

DISCUSSION

The COVID-19, which has become a worldwide pandemic since December 2019, shows a mild course in childhood compared to adults (8). The majority of pediatric patients with a positive PCR test for COVID-19 had an asymptomatic course, yet only 2% required hospitalization in the intensive care unit (9). This disease is spreading rapidly worldwide and new mutations in viral RNA are emerging, which changes the severity of the disease in pediatric patients and increases the need for intensive care unit admissions. In order to determine an investigative, therapeutic and follow-up strategy for patients hospitalized in the PICU, we identified the COVID-19 patients who were followed up in our intensive care unit to date. The factors affecting the prognosis of the patients, the changes in the course of the disease and supportive treatments were determined. Children of all age groups are susceptible to SARS-CoV-2 infection, but have milder clinical manifestations than adults. In pediatric patients, Covid-19 is most often observed under the age of 3 years, with a slight predominance of the male gender (10). In this study, the mean age of patients with COVID-19 admitted to the PICU was 126,5 (37-185) month, with no gender difference between patients. It was detected more frequently in young children, which was consistent with other literature studies (11). The lower frequency, especially in younger ages, can be attributed to the role of the immune system in improving the clinical picture. Comorbidities are the most important risk factors for critical illness in pediatric COVID-19 patients (11). In our study, the most common comorbidity was neurological disorders, followed by metabolic, cardiac and respiratory disorders.

The initiation of quarantine and active surveillance of suspected patients, and the use of rapid detection tools to confirm the etiology of the disease are strongly recommended. COVID-19 is a highly contagious disease. However, 75-80% of patients have a mild disease course. Patients with two or more comorbidities such as diabetes or malignancy tend to have higher morbidity or mortality rates (12,13). Our study, in particular, showed a higher frequency of comorbidities. Less than half of our patients had lower rates of contact history compared to previous studies. This is attributed to the lack of testing for COVID-19 in all children and to a mild course of the disease.

Children are reported to have a milder course of SARS-CoV-2, however, patients admitted to the PICU appear to have a severe course of the disease. Consistent with the literature, the most common symptoms in our study were dispnea (64.2%), fever (53.7%) and cough (52.4%), respectively (12). In some cases, patients are admitted to the PICU with severe respiratory distress, cyanosis, fever and cough, and may even develop respiratory and circulatory failure during hospitalization. In our study, approximately 50% of our patients developed hypoxia and were supported by oxygen therapy. The high frequency of respiratory and circulatory failure in COVID-19 positive patients is especially associated with the high incidence of comorbid conditions, which is one of the most important reasons for admission to the PICU. About half of the COVID-19 positive patients had a concurrent congenital or acquired disease. This causes different disease presentations, especially ARDS. However, in our study, comorbidities and organ

dysfunctions such as respiratory or circulatory failure, with a higher frequency in young children, caused a more severe clinical course.

As in other publications, COVID-19 positive patients in our study had leukopenia, lymphopenia and elevated CRP levels. Our study showed comparable rates of coagulation disorders and troponin elevations with literature studies (13,14). Although many studies have reported lymphopenia, leukopenia, thrombocytopenia, and elevated CRP levels, these have not been proven to be disease-specific criteria (15). Chest X-rays are the first preferred radiological diagnosis method in suspected pulmonary involvement. Peribronchial thickening and multifocal ground-glass infiltrates are the most common chest X-ray examination findings of COVID-19 pneumonia in children. (16). In this study, half of the chest X-rays revealed normal, but the most common radiographic findings included multifocal or diffuse ground glass infiltrations and/or consolidations and unilateral peripheral or peripheral-central ground glass infiltrations and/or consolidations. Chest X-rays are the first-line imaging study in patients with suspected COVID-19 infection. Despite this fact, studies in the literature have reported a relatively low rate of chest X-ray findings in patients with COVID-19.

Computed tomographic examination has a limited role in COVID-19 pneumonia in children. In our study, CT imaging yielded normal results in most pediatric patients, with the highest frequency of peripheral ground-glass infiltrates, cobblestone appearance, halo, and reversed halo findings (17,18). The most common findings in the patients in our study were multifocal or diffuse ground glass infiltration and/or consolidation and prominent peripheral ground glass infiltration and/or consolidation in the lower lobes.

There is no intensive therapy for pediatric patients, which is more often preferable to supportive symptomatic therapy, which included free oxygen support in approximately 77% of patients, antiviral therapy in 63% of severe cases, and prophylactic antibiotic therapy in 97%. Antiviral therapy and supportive therapy were started immediately in patients admitted to the PICU. The early initiation of treatment is due to the high complication and mortality rates in adults with COVID-19 and the lack of sufficient number of studies in pediatric patients. However, at the beginning of the pandemic in our country, drug combinations such as hydroxychloroquine, azithromycin, favipravir, lopinavir/ritonavir were used in patients who applied with the suspicion of COVID-19 and had evidence on thoracic CT imaging and complications (such as PARDS, septic shock, MODS, TAMOF). No specific antiviral efficacy of these agents has been demonstrated based on currently available data. Hydroxychloroquine and chloroquine have been shown to have anti-SARS-CoV-2 activities in in vitro studies (19,20). It is an appropriate approach to start treatment before the development of multiple organ dysfunction syndrome. Our goal in initiating an early treatment with these drugs was to prevent disease progression and the need for mechanical ventilatory support. Indications for antiviral therapy (Hydroxychloroquine, or Lopinavir / Ritonavir) in patients with suspected or confirmed COVID-19 infection included severe pneumonia (PARDS) or critical illness (SHOCK, TAMOF, DIC, Hemophagocytic syndrome). These patients were also given IVIG, steroids, plasmapheresis and RRT. Of the patients with severe PARDS, 6 received immune plasma therapy and 12 died. One patient with Steven Johnson syndrome who developed severe ARDS was supported by V-V ECMO and died 3 weeks later. None of the treatments have shown a clear benefit for COVID-19 infection, and the World Health Organization does not recommend any specific treatment for pediatric patients (21). Respiratory support therapies such as HFNC and NIV were preferred in 60% of COVID-19 positive patients to prevent the development of respiratory failure. These respiratory support therapies were used more cautiously in COVID-19 positive patients due to the generation of aerosols and the risk of transmission. In our study, mechanical ventilatory support was provided to patients with low SaO_2 and elevated OSI levels and the need to obtain high FiO_2 levels. We provided invasive and non-invasive respiratory support to 59.5% of the patients. Of the patients, 35.4% (n=28) worsened or were intubated while on HFNC or NIV supports. Studies in the literature have reported an intubation rate of 15-47% in COVID-19 positive patients admitted to the PICU, which is comparable to our study (22,23,24,25), but still lower than in adults (26,27)

High PRISM and PELOD scores due to respiratory and circulatory failure, and the need for invasive and aggressive treatments such as immune plasma therapy, RRT, plasmapheresis, and ECMO support were associated with poor prognosis and high mortality rates in patients with COVID-19.

CONCLUSION

The majority of COVID-19 patients admitted to the PICU had respiratory failure. A multidisciplinary approach is needed in COVID-19 patients. In line with previous studies, our study aimed to contribute to the literature in order to fill the diagnostic gap through clinical findings, laboratory values and chest radiographic examinations in COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of the Ministry of Health dated 14 May 2020 (Ethics committee 20-567) and the approval of the local ethics committee (Ethics committee number: 567).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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