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# Evaluation of Clinical Features and Treatment Results of Pediatric Patients With Pre-Diagnosis of COVID-19

COVID-19 Ön Tanısı Olan Çocuk Hastaların Klinik Özellikleri ile Tedavi Sonuçlarının Değerlendirilmesi

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**ABSTRACT**

**Aim:** The epidemiological characteristics and modes of transmission of coronavirus disease 2019 (COVID-19) in children are not yet fully understood. In this study, it was aimed to evaluate clinical, laboratory, and radiological findings and treatment approaches in patients with negative and positive PCR tests among those with suspected COVID-19 retrospectively.
**Material and Methods:** This study was conducted with 317 patients under 18 years of age, who received outpatient or inpatient treatment with a pre-diagnosis of COVID-19. All patients were assessed for clinical course, disease severity, comorbidity, demographic characteristics, laboratory and radiodiagnostic tests, treatment characteristics, and outcomes.
**Results:** The PCR test was positive in 133 (42%) and negative in 184 (58%) of the patients with suspected COVID-19. There was a history of contact in 78 (58.6%) and 51 (27.7%) of the PCR-positive and negative patients, respectively (p<0.001). While the PCR-negative group had a higher rate of hospitalization (p=0.020), hospital stay was longer in PCR-positive cases (p=0.037). The white blood cell count (p=0.001), platelet count (p=0.037), neutrophil count (p=0.015), and lactate level (p=0.025) were significantly lower in the PCR-positive group.
**Conclusion:** Early detection and isolation of children with symptoms suggestive of COVID-19 are important to limit the spread of the disease. It can be challenging initially to clinically understand whether the case has COVID-19, especially in pediatric patients. PCR test is the gold standard in the diagnosis of COVID-19. Considering the prevalence, severity, and complications of the outbreak, it would be a proper approach to initially evaluate suspected patients as COVID-19 patients.
**Keywords:** COVID-19; childhood; SARS-CoV-2.

**ÖZ**

**Amaç:** Çocuklarda koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19)'un epidemiyolojik özellikleri ve bulaşma yolları henüz tam olarak anlaşılamamıştır. Bu çalışmada, COVID-19 şüphesiyle takip edilen PCR testi negatif ve pozitif olan hastalarda klinik, laboratuvar ve radyolojik bulgular ve tedavi yaklaşımlarının geriye dönük olarak değerlendirilmesi amaçlanmıştır.
**Gereç ve Yöntemler:** Bu çalışma, COVID-19 ön tanısı ile ayaktan veya yatarak tedavi gören 18 yaş altı 317 hasta ile yapılmıştır. Tüm hastalar klinik seyir, hastalık şiddeti, ek hastalıkları, demografik özellikler, laboratuvar ve radyodiagnostik testler, tedavi özellikleri ve sonuçları açısından değerlendirildi.
**Bulgular:** COVID-19 şüphesi olan hastaların 133'ünde (%42) PCR testi pozitif ve 184'ünde (%58) negatifti. PCR pozitif ve negatif hastaların sırasıyla 78'inde (%58,6) ve 51'inde (%27,7) temas öyküsü vardı (p<0,001). PCR-negatif grupta hastaneye yatış oranı daha yüksek iken (p=0,020), PCR-pozitif grupta hastanede kalış süresi daha uzundu (p=0,037). Beyaz kan hücresi sayısı (p=0,001), trombosit sayısı (p=0,037), nötrofil sayısı (p=0,015) ve laktat düzeyi (p=0,025) PCR pozitif grupta anlamlı düzeyde düşüktü.
**Sonuç:** COVID-19'u düşündüren semptomları olan çocukların erken tespiti ve izolasyonu, hastalığın yayılmasını sınırlamak için önemlidir. Özellikle pediatrik hastalarda vakanın COVID-19 olup olmadığını klinik olarak anlamak başlangıçta zor olabilir. PCR testi COVID-19 tanısında altın standarttır. Salgının yaygınlığı, şiddeti ve komplikasyonları göz önüne alındığında şüpheli hastaları başlangıçta COVID-19 hastası gibi değerlendirmek uygun bir yaklaşım olacaktır.
**Anahtar kelimeler:** COVID-19; çocukluk çağı; SARS-CoV-2.

## INTRODUCTION

In December 2019, cases of pneumonia of unknown etiology began to occur in Wuhan, Hubei province of China (1). The disease rapidly spread to other parts of China and several countries across the world. Later, a new member of the enveloped RNA coronavirus family was identified in bronchoalveolar lavage fluid samples collected from a patient in Wuhan and was accepted as the causative agent of this disease by the Chinese Center for Disease Control and Prevention (2). The World Health Organization (WHO) named this virus as the 2019 novel coronavirus (2019-nCoV) and the disease as coronavirus disease 2019 (COVID-19).

The first case detected in Europe was reported in France on January 24, 2020, followed by case reports in many European countries (3). Turkey reported its first case of COVID-19 on March 10, 2020 (4).

The first pediatric case diagnosed with COVID-19 was reported in Shenzhen on January 20, 2020 (5). After this date, cases have been increasingly reported worldwide. The epidemiological characteristics and modes of transmission of COVID-19 in children are not yet fully understood. Center for Disease Control and Prevention has reported that only 2% of cases occur in individuals younger than 19 years (6). According to United States data, pediatric patients account for 1.7% of the cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (7). These data suggest that children are less affected by 2019-nCoV, unlike other viruses. Clinical findings in pediatric patients are atypical and relatively milder than in adult patients. Children are mostly asymptomatic. Some cases have upper respiratory symptoms such as fever, dry cough, malaise, runny nose, and nasal congestion. Gastrointestinal symptoms such as abdominal pain, nausea-vomiting, and diarrhea may also be observed (8).

Although COVID-19 is diagnosed according to certain criteria, it can be challenging to diagnose the disease in PCR-negative patients. Even if there is a strong clinical suspicion, it is important to have other criteria for diagnosis in PCR test negativity. The present study evaluated clinical, laboratory, and radiological findings and treatment approaches in patients with negative and positive PCR test results among those with suspected COVID-19. The COVID-19-related findings were comparatively evaluated according to the laboratory and clinical characteristics of the patients.

## MATERIAL AND METHODS

This single-centered retrospective study was conducted with 317 patients under 18 years of age, who received outpatient or inpatient treatment with a pre-diagnosis of COVID-19. This study was approved by the Ethics Committee of Düzce University (07.12.2020, 258). The study included both patients with a positive PCR test and patients tested for suspected SARS-CoV-2 and had a negative PCR test. The medical records of the patients were reviewed. Patients above 18 years of age, with inaccessible files or with severely incomplete data were excluded from the study. All patients were assessed for epidemiological and demographic characteristics, laboratory and radiodiagnostic tests, and treatment characteristics and outcomes. In addition, fever, cough, tachypnea, tachycardia, hypoxia, sore throat, fatigue, myalgia, headache, vomiting, diarrhea, and loss of smell were examined. Complete blood count, serum biochemical tests, myocardial enzymes, coagulation tests, erythrocyte sedimentation rate, and C-reactive protein (CRP) levels of the patients were evaluated. Patients with respiratory complaints or suspected pneumonia on physical examination received PA chest X-ray and those with unexplained respiratory findings or poor clinical course received lung computed tomography (CT) as an additional test.

Patients with at least one of the conditions such as hypoxia (oxygen saturation <92%), tachypnea, loss of consciousness, coma, convulsions, dehydration, feeding difficulties, vomiting, diarrhea, findings of myocardial injury, elevated liver enzymes, coagulation disorders, and rhabdomyolysis were admitted to the hospital. Among these patients, those without any improvement upon treatment and with worsening general condition were admitted to the intensive care unit. The treatment protocol for inpatients included general supportive treatment, monitoring of lung, liver, kidney, and heart functions, fever management, and oxygen delivery at a rate of 2-4 l/min via nasal cannula, systemic corticosteroids, and inhaled corticosteroids for patients with a saturation of <92%. Patients with indications were initiated on oseltamivir therapy and/or antibiotherapy (Ceftriaxone/Cefotaxime/Azithromycin). Azithromycin was added to the treatment of outpatients in the presence of secondary bacterial infection.

### Polymerase Chain Reaction (PCR) Method

Combined nasopharyngeal-oropharyngeal swab, sputum, or tracheal aspirate samples were collected from suspected cases of COVID-19. The samples were sent to the laboratory under appropriate conditions in a viral transport medium, where they were processed in the biosafety cabinet. Nucleic acid extractions were performed manually using Bio-speedy viral nucleic acid extraction buffer (Bioeksen R&D Technologies, Turkey). PCR testing was then performed using a SARS-CoV-2 (2019-nCoV) RT-qPCR detection kit (Bioeksen R&D Technologies, Turkey) and Montania® Real-Time PCR instruments (Anatolia Geneworks, Turkey). PCR test results were evaluated and reported by the same laboratory manager.

### Statistical Analysis

The distribution of the data was analyzed by the Kolmogorov-Smirnov test, and the Independent Samples t-test or the Mann-Whitney U test were used to compare the groups, depending on the distribution. Categorical variables were analyzed by Pearson chi-square, Fisher's exact, or Fisher-Freeman-Halton tests, depending on the expected count. Correlations among quantitative variables were examined by Pearson or Spearman correlation analysis, depending on the distribution of the variable. Descriptive statistics of the data were expressed as mean±standard deviation or median, quartiles, and minimum-maximum values, while categorical variables were summarized as frequency and percentage. Statistical analyses were performed using IBM SPSS v.22 software. The statistical significance level was considered as a p value of less than 0.05.

## RESULTS

Among 317 children included in the study, the PCR test was positive in 133 (42%) and negative in 184 (58%). There was no significant difference in age (p=0.529) and gender (p=0.854) between PCR-positive and negative patients. There was a history of contact in 27.7% (n=51) and 58.6% (n=78) of PCR-negative and positive patients, respectively (p<0.001). The PCR-negative group had a higher rate of hospitalization (p=0.020). On the other hand, hospital stay was longer in PCR-positive cases than in negative ones (p=0.037). Oral, IV, or inhaled treatment was required in 59.8% (n=110) and 57.1% (n=76) of PCR-negative and positive cases, respectively (Table 1).

The comparison of the patients' clinical findings revealed that fever was more common in PCR-positive patients, while there was no significant difference in pulmonary involvement, cough, tachypnea, tachycardia, hypoxia, sore throat, fatigue, myalgia, headache, GI involvement findings, and additional chronic diseases between the groups. The PCR-positive and negative cases had similar comorbidity rates. These comorbidities were asthma, epilepsy, familial Mediterranean fever, hyperthyroidism, congenital adrenal hyperplasia, obesity, scoliosis, Tip 1 diabetes mellitus, prematurity, and cerebral palsy.

Peribronchial infiltration and consolidation were observed as chest X-ray findings, and the findings in positive and negative cases were similar. The lung tomography findings of ground glass, consolidation, empyema, and atelectasis were also similar in both groups of patients.

The white blood cell (WBC) count (p=0.010), platelet count (p=0.037), neutrophil count (p=0.015), and lactate level (p=0.025) were statistically significantly lower in the PCR-positive group (Table 2).

Age and the occurrence of disease symptoms (sore throat, myalgia, headache, and loss of smell) were positively correlated in PCR-positive patients (r=0.384, p=0.034). However, this correlation was not found in PCR-negative patients. Similarly, it was observed that the frequency of symptoms increased with increasing age in PCR-positive patients. On the other hand, both WBC (r=-0419, p<0.001) and lymphocyte counts (r=-0578, p<0.001) decreased with increasing age in PCR-positive COVID-19 patients.

Multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, one of the important complications of the disease, was detected in three of the PCR-positive patients, while only two of them required hospitalization. All of the outpatients and inpatients recovered. These patients were excluded from the study.

The presence of additional chronic diseases is a risk factor for COVID-19. Depending on the severity of the disease, it can directly affect mortality and morbidity. The comparison of the patients related to additional chronic diseases was presented in Table 3.

When the symptoms and findings of the patients were evaluated by gender, sore throat was more common in females, while creatine kinase (CK) level was higher in males. Regarding all other parameters, there was no significant difference in gender between the two groups.

## DISCUSSION

COVID-19 is an important disease that has affected the whole world and caused serious mortality and morbidity. Information about the occurrence and course of the disease in children has yet to be revealed. The present study assessed clinical and laboratory characteristics, treatment methods, and other disease-related factors in PCR-positive and negative cases among pediatric patients with suspected COVID-19 who presented with acute upper or lower respiratory tract infection symptoms.

**Table 1.** Demographic and clinical characteristics of PCR-positive and PCR-negative patients

| | **PCR-positive (n=133)** | **PCR-negative (n=184)** | **p** |
|---|---|---|---|
| **Age** (year), mean±SD | 8.66±6.18 | 8.24±5.76 | 0.529 |
| **Gender**, n (%) | | | |
| Male | 65 (48.9) | 88 (47.8) | 0.854 |
| Female | 68 (51.1) | 96 (52.2) | |
| **History of patient contact**, n (%) | 78 (58.6) | 51 (27.7) | **<0.001** |
| **Hospitalization rate**, n (%) | 4 (3.0) | 17 (9.2) | **0.028** |
| **Length of hospital stay** (day), median (IQR) [min-max] | 11 (13) [4-18] | 3 (4) [1-11] | **0.037** |
| **Fever**, n (%) | 72 (54.1) | 71 (38.6) | **0.006** |
| **Cough**, n (%) | 39 (29.3) | 44 (23.9) | 0.280 |
| **Tachypnea**, n (%) | 6 (4.5) | 7 (3.8) | 0.754 |
| **Tachycardia**, n (%) | 2 (1.5) | 2 (1.1) | 0.743 |
| **Hypoxia**, n (%) | 3 (2.3) | 4 (2.2) | 0.961 |
| **Comorbidity**, n (%) | 19 (14.3) | 27 (14.7) | 0.923 |
| **X-Ray**, n (%) | | | |
| Normal | 101 (75.9) | 144 (78.3) | 0.447 |
| Peribronchial infiltration | 30 (22.6) | 33 (17.9) | |
| Consolidation | 2 (1.5) | 6 (3.3) | |
| Empyema | 0 (0.0) | 1 (0.5) | |
| **Medication** (n=76 vs n=111), n (%) | | | |
| Antibiotic | 64 (84.2) | 103 (92.8) | 0.148 |
| Antibiotic + Antiviral | 10 (13.2) | 6 (5.4) | |
| Corticosteroid | 1 (1.3) | 2 (1.8) | |
| Corticosteroid + Acetyl salicylic acid | 1 (1.3) | 0 (0.0) | |

SD: standard deviation, IQR: interquartile range

**Table 2.** Laboratory parameters of PCR-positive and PCR-negative patients

| | PCR-positive (n=133) | PCR-negative (n=184) | p |
|---|---|---|---|
| **WBC** ($10^3$/ul), median (IQR) [min-max] | 7.2 (4.4) [2.7-21.6] | 8.6 (6.0) [2.1-25.1] | **0.001** |
| **RBC** ($10^6$/ul), mean±SD | 4.61±0.53 | 4.66±0.52 | 0.441 |
| **RDW** (%), mean±SD | 13.91±1.68 | 14.03±1.78 | 0.611 |
| **Platelet** ($10^3$/ul), median (IQR) [min-max] | 269 (107) [68-624] | 282 (108) [107-633] | **0.037** |
| **Lymphocyte** ($10^3$/ul), median (IQR) [min-max] | 1.86 (1.69) [0.4-7.11] | 2.14 (1.85 [0.3-8.24] | 0.654 |
| **Neutrophil** ($10^3$/ul), median (IQR) [min-max] | 4.21 (3.70) [0.39-13.02] | 4.70 (5.83) [0.62-22.52] | **0.015** |
| **NLR**, median (IQR) [min-max] | 1.79 (2.03) [0.12-18.06] | 2.28 (4.17) [0.02-58.61] | 0.195 |
| **PLR**, median (IQR) [min-max] | 128.83 (93.99) [27.71-480] | 128.91 (134.33) [30.07-580] | 0.690 |
| **Uric acid** (mg/dl), mean±SD | 3.95±1.13 | 3.73±1.37 | 0.245 |
| **CRP** (mg/dl), median (IQR) [min-max] | 0.39 (0.71) [0.06-18.97] | 0.35 (2.41) [0.01-25.90] | 0.935 |
| **Urea** (mg/dl), mean±SD | 20.68±7.35 | 22.00±7.43 | 0.195 |
| **BUN** (mg/dl), mean±SD | 9.91±3.52 | 10.42±3.42 | 0.288 |
| **Creatinine** (mg/dl), mean±SD | 0.54±0.19 | 0.53±0.18 | 0.567 |
| **AST** (IU/l), median (IQR) [min-max] | 29.5 (20.9) [11.8-127.6] | 28.1 (13.5) [10.7-180.7] | 0.602 |
| **ALT** (U/ml), median (IQR) [min-max] | 14.1 (12.3) [5.6-85.2] | 14.1 (8.6) [4.6-117.9] | 0.933 |
| **Phosphorus** (mg/dl), mean±SD | 4.70±1.08 | 4.51±0.96 | 0.188 |
| **Lactate** (mg/dl), mean±SD | 1.69±0.67 | 3.12±1.28 | **0.025** |
| **LDH** (U/l), mean±SD | 257.68±78.39 | 265.13±62.57 | 0.674 |
| **Procalcitonin**, median (IQR) [min-max] | 0.07 (0.31) [0.03-4.67] | 0.27 (0.26) [0.02-20.77] | 0.233 |
| **ESR** (mm/h), median (IQR) [min-max] | 16 (19) [8-60] | 19 (32) [2-140] | 0.472 |
| **CK** (mg/dl), median (IQR) [min-max] | 109 (103) [19-302] | 81 (67) [16-299] | 0.589 |
| **CK-mb** (IU/l), median (IQR) [min-max] | 22.5 (31.9) [4-58] | 29.0 (15.8) [15-74] | 0.295 |
| **PT** (sn), median (IQR) [min-max] | 9.71 (3.29) [1.04-13.70] | 9.96 (9.89) [1.08-68.60] | 0.978 |
| **aPTT** (sn), mean±SD | 28.89±4.75 | 30.18±5.38 | 0.418 |
| **D-dimer** (mcg/ml), median (IQR) [min-max] | 0.26 (0.41) [0.02-9.29] | 0.33 (0.61) [0.20-3.43] | 0.401 |
| **Vitamin D** (ng/ml), median (IQR) [min-max] | 17.71 (15) [7.40-50.35] | 22.43 (13.15) [5.61-53.40] | 0.160 |

WBC: white blood cell, RBC: red blood cell, RDW: red cell distribution width, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, CRP: C-reactive protein, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate, CK: creatine kinase, PT: prothrombin time, aPTT: activated partial thromboplastin time, SD: standard deviation, IQR: interquartile range

**Table 3.** Demographic and clinical characteristics of the PCR-positive patients according to the comorbidity

| Comorbidity | Yes (n=19) | No (n=114) | p |
|---|---|---|---|
| **Age** (years), mean±SD | 12.00±5.22 | 8.11±6.17 | **0.010** |
| **Gender**, n (%) | | | |
| Male | 8 (42.1) | 57 (50.0) | 0.524 |
| Female | 11 (57.9) | 57 (50.0) | |
| **History of patient contact**, n (%) | 7 (36.8) | 71 (62.3) | **0.037** |
| **Hospitalization rate**, n (%) | 1 (5.3) | 3 (2.6) | 0.464 |
| **Tachypnea**, n (%) | 4 (21.1) | 2 (1.8) | **0.004** |
| **Normal CT findings**, n (%) | 17 (89.5) | 114 (100) | **0.019** |

SD: standard deviation, CT: computed tomography

The reason COVID-19 is less severe in children than in adult patients has not yet been fully clarified. This may be related to both less viral exposure and host factors. Being in less contact with patients and being in a relatively more isolated environment compared to adults are important factors for the prevention of the disease in children. The risk of transmission is further reduced, especially with isolation measures. Children who have been out of the school environment and have an isolated life at home are less likely to catch the disease. Considering the host effect, factors related to angiotensin-converting enzyme II (ACE2) become prominent. This enzyme has been shown to be a cell receptor for the SARS-CoV (9). There is amino acid homology between 2019-nCoV and SARS-CoV, and ACE2 has been identified as the cell receptor of 2019-nCoV, like SARS-CoV (10). Since the level of ACE2 maturity and function (for example, the ability to bind) may be lower in children than in adults, it is estimated that children are less likely to be infected with 2019-nCoV (11). However, the severity of COVID-19 symptoms may change with age due to differences in ACE2 expression, lymphocyte count, and acquired immunity (12). On the other hand, ACE2 may increase especially in children entering adolescence (13). The lack of difference in age and disease severity between PCR-positive and negative pediatric patients in the present study, unlike adult patients, may be related to the study patient group that included younger patients who had not yet entered adolescence. Another prominent factor is the increased incidence of viral infections in children in winter. Children often have respiratory infections, for example, respiratory syncytial virus (RSV), during the winter and have higher levels of antibodies against viruses than adults do (14). Furthermore, the immune system of children is still developing and therefore their response to pathogens may differ from those of adults.

Studies have revealed that history of contact is a significant risk factor for the COVID-19 outbreak (15). The low incidence of COVID-19 in children can be explained by their fewer contacts. The more common history of contact in SARS-CoV-2 positive children compared to negative children in the present study suggests that the disease is transmitted by contact in children, like in adults.

Admission to the intensive care unit is considered a direct indicator of a more severe course of the disease. Prior studies with pediatric patients report different results regarding the rate of critically ill patients admitted to the intensive care unit. A previous study observed that 13 of 67 SARS-CoV-2 positive pediatric patients presenting to the emergency department needed intensive care. It was reported that cough and shortness of breath were the major symptoms among these patients, and they were considered severe cases and admitted to the intensive care unit (16). Another study found the rate of SARS-CoV-2 positive pediatric patients admitted to the intensive care unit to be 16% (17). The number of critical cases among the patients included in this study was 3%. None of the PCR-negative patients who were admitted to the hospital due to suspected COVID-19 were indicated for intensive care. Even if the patient is clinically suspected to have COVID-19, the PCR test is considered important data for diagnosing the disease and understanding the severity. In addition, hospital stay was longer in PCR-positive children with COVID-19 than in those who were PCR-negative. When the patients were evaluated considering both the length of hospital stay and indications for intensive care, the disease was found to progress more severely in children with COVID-19 compared to those with a negative PCR test.

Viruses are the most common cause of acute respiratory tract infections in children and the etiological agents differ according to the age and immunity of the patient. Imaging also shows different findings according to the etiological agent. CT can provide valuable information for the diagnosis of respiratory tract infections. The type of viral pathogen, the immune status of the host, and the pathogenicity of the viral agent may alter CT findings. Clinical and CT findings of many respiratory viral pathogens such as influenza, human parainfluenza virus, RSV, rhinovirus, and adenovirus have been described. In general, causative agents of respiratory viral infections lead to lung CT findings such as bronchial wall thickening, multifocal consolidation, or ground-glass opacity. When a bacterial infection develops secondary to viral pneumonia, distinctive findings such as diffuse air-space patterns can be observed (18). In the present study, the lung CT findings did not significantly differ between PCR-negative and positive cases. Although PCR is an important marker for diagnosing SARS-CoV-2, it is controversial that PCR negativity can completely exclude the disease. The CT findings of PCR-negative cases being similar to positive cases increase the importance of the PCR test in diagnosis. However, the rate of COVID-19 but PCR-negative cases can also be quite high. Fang et al. (19) reported that the rate of false-negative PCR could increase up to 30%. Another study indicated that an initially negative PCR test might turn positive in repeated testing (20). The present study could not assess the rate of false negativity because PCR-negative patients among the study patients were not tested again. However, similar CT findings suggest that PCR-negative patients might also have COVID-19. We believe that approaching patients as SARS-CoV-2 positive cases until proven otherwise if there is clinical suspicion would be an approach both to increase the success of treatment and to reduce the spread of the disease. On the other hand, it should be kept in mind that other viral agents may also lead to CT findings similar to COVID-19.

Studies with adults have reported that gender might be a significant risk factor for COVID-19 and might affect the severity of the disease. Expression of ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) are believed to be factors effective in the entry of the virus into the cell. These factors may also cause the disease to present different characteristics by gender. However, Mukherjee et al. (21) reported that individual behavioral differences, habits such as smoking, and comorbidities might also affect gender-related differences. Di Stadio et al. (22) stated that the lower prevalence and milder course of COVID-19 in women might be related to the effect of estrogen. According to the researchers, estrogen stimulates the immune system by modulating the functions of B cells and improving the activity of T-helper-2 cells, this effect occurs especially in the upper respiratory tract mucosa, thereby preventing the virus from entering the body and spreading. However, studies show no gender differences in the prevalence and severity of the disease in children (23). The present study also obtained similar results. Apart from genetic predisposition, the lower prevalence of COVID-19 in children can be explained by habits and comorbidities being less common in children compared to adults. Furthermore, the hormonal effect-related factors do not occur since they have not yet entered puberty. Due to all these factors, gender differences may not be observed in pediatric patients with COVID-19.

Comparison of the study group by hematological parameters revealed that WBC and neutrophil counts were statistically significantly lower in PCR-positive patients, but none of the cases were neutropenic. Neutrophils are the most important cellular defense mechanism against infections, which are the first to respond to viral invasion and limit viral replication and spread. Nevertheless, neutrophils are also known to mediate detrimental effects on the host during viral infection (24). A previous study showed that an elevated neutrophil count was associated with the development of acute respiratory distress syndrome (ARDS) and an increased risk of mortality in adults with COVID-19 (25). Accordingly, it can be predicted that patients without neutrophilia would have a milder course of the disease. In the present study, the neutrophil count of the patients did not increase, and most of the cases survived the disease with a mild course. On the other hand, the immune response to a viral infection is primarily mediated by lymphocytes. It is hypothesized that the decreased lymphocyte count may be due to increased lymphocyte consumption, destruction of lymphatic tissues, and cytokine-related T cell apoptosis in COVID-19 patients (26). It has been shown that 2019-nCoV binds to the ACE2 receptor on the lymphocyte surface, infiltrating the lymphocyte and causing lymphopenia (27). Thus, the lymphocyte count decreases with the increasing severity of the disease. While lymphopenia is considered an important prognostic criterion in adult patients, it is a controversial issue in pediatric patients. Some papers have reported a relationship between lymphopenia and disease severity, while others could not demonstrate such a relationship (28,29). The less severe course of the disease in pediatric patients unlike in adults can be explained by the less severe inflammation, the lower levels of cytokine activation, and the non-development of lymphopenia due to the immature immune system. It was not possible to associate the changes in leukocyte and lymphocyte counts with the severity of the disease because only two patients had a severe course in the study group. In addition, there were no significant changes in lymphocyte and leukocyte counts of these two patients. On the other hand, studies have reported that an increase in the neutrophil-to-lymphocyte ratio is a negative prognostic indicator for hospitalized patients (30). The lack of any difference in this respect in the patient group can be explained by the mild course in most cases.

Although the platelet count was statistically significantly lower in PCR-positive cases than in negative cases, platelet counts were within normal limits in both groups. Changes in platelet count and activity are closely associated with various diseases (31). Platelets not only contribute to hemostasis but are also involved in inflammation and host defense. Decreased production and increased consumption of platelets due to diffuse alveolar damage are believed to cause thrombocytopenia in COVID-19 patients (23). However, this may occur in patients with a severe course and high mortality.

The present study found a higher lactate level in PCR-negative patients than in positive patients; however, there was no clinical difference in disease severity between the groups. Lactate measurement is used in the assessment of critically ill patients as an indicator of both disease severity and mortality. Lactate accumulates in a state of anaerobic metabolism and reflects the degree of tissue hypoxia due to poor perfusion (32). Hyperlactatemia occurs in trauma, hypoxemia, severe anemia, and septic shock (33). In critically ill children with sepsis, hyperlactatemia on admission is associated with high mortality (32). However, research has not yet clarified the clinical impact of changes in serum lactate levels in patients with COVID-19. It is believed that the present study could not obtain any significant result regarding lactate levels due to the low number of severe patients.

Severe rhabdomyolysis cases associated with COVID-19 have been reported in the literature as case reports (23,34). Some studies from China reported patients with elevated levels of CK without developing rhabdomyolysis. A study of 95 adult patients established various levels of CK elevation in 28 patients (35). Another study found high CK levels in 10% of adult patients (36). In children, CK elevation associated with COVID-19 is a rare finding. A study on CK levels in this age group reported that there was only one patient with elevated CK and none of the patients developed rhabdomyolysis (37). In general, viral rhabdomyolysis occurs due to direct viral invasion of the muscle, cytokine storm resulting in muscle damage, and muscle injury caused by circulating viral toxins (34). Chen et al. (38) have suggested that rhabdomyolysis associated with COVID-19 is secondary to cytokine storm due to the presence of elevated inflammatory markers and the absence of viral particles in muscle biopsies. The present study detected a moderate level of CK elevation in eight of the males and only one of the females in the PCR-positive patient group. None of these patients were seriously ill and indicated for intensive care. Cytokine storm is an important complication in COVID-19 that aggravates the clinical picture. However, the disease does not usually progress severely in these patients, suggesting that CK elevation may be due to reasons other than cytokine storm. There is not enough information about this subject in the literature. It is believed that the higher incidence of CK elevation in the males in the study was a coincidental finding rather than sex-related differences. Nevertheless, the CK levels of the patients under follow-up did not increase very much and returned to normal levels in a short time, indicating the clinical insignificance of this elevation.

This study had some limitations. The study only included patients presenting to a healthcare facility, which is a limitation. The patients were not re-evaluated for clinical and laboratory findings after discharge, and no comparison could be made with the disease findings. The third limitation was that the suspected cases were more serious and critical than patients with confirmed COVID-19. This suggests that some of the PCR-negative patients might also have COVID-19. However, other viral serological studies could not be performed for PCR-negative patients. Therefore, the presence of an infection other than COVID-19 could also not be demonstrated in these patients.

## CONCLUSION

Early detection and isolation of children with symptoms suggestive of COVID-19 are important to limit the spread of the disease. Although the PCR test is the best diagnostic tool, it could not provide clear information to diagnose the disease. Low viral load, inappropriate specimen type, suboptimal specimen collection, and low analytic sensitivity may be related to false negative PCR test. Considering the prevalence, severity, and complications of the outbreak, it would be a proper approach to initially evaluate suspected patients as COVID-19 patients even if the PCR is negative. As the number of cases increases, more detailed and clear information about COVID-19 will be available. There is a need for studies with broad participation and post-recovery assessment, especially to explain the different courses of the disease between children and adults.

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